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The Journal of Allergy

VOL. 16 JANUARY, 1945 No. 1

Original Articles

ENDOCRINE ALLERGY*

I. ALLERGIC SENSITIVITY TO ENDOGENOUS HORMONES

BERNHARD ZONDEK, M.D., AND Y. M. BROMBERG, M.D., JERUSALEM

ALLERGIC reactions are generally elicited by exogenic allergens. Nevertheless, evidence has been brought forward that allergens may also arise within the body as products of diseased or functionally altered organs.[1, 2] In the present paper, evidence is advanced that allergic reactions may also be due to endogenous allergens produced within the organism by endocrine glands. It will be shown that certain pathologic disturbances are due to a sensitivity on the part of the organism to various of its hormones and the products of their metabolism. We propose for this condition the name "endocrine allergy."

The above conclusion is supported by the following clinical observations.

1. In certain cases, injections of estrone or estradiol benzoate induce general symptoms, such as nausea, vomiting, fever, diarrhea, urticaria, etc.

2. In some cases of pruritus vulvae, administration of estrogenic hormone gives relief only if given in low dosage; large doses in such cases may cause severe exacerbation of the disease. The successful treatment of pruritus vulvae, by percutaneous application of small quantities of sex hormones (Zondek[3]), is plausibly explained as a consequence of desensitization through continuous absorption of hormone in minimal quantities.

3. Certain allergic diseases (asthma, angioneurotic edema, urticaria, migraine, etc.) take a particularly severe form during the premenstrual phase in which production of the follicle and corpus luteum hormones reaches maximal levels.

It follows, from the assumption that endogenous hormones may act as endogenous allergens, that a subject allergic to estradiol or testos-

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*This work was aided by a grant from the Ella Sachs Plotz Foundation.

terone will react with general symptoms when large doses of these hormones are administered. It is therefore comprehensible that, in the treatment of pruritus vulvae, large doses of hormone may have harmful effects on a sensitized patient, whereas small doses in the same case give good results through gradual desensitization.

Several years ago the senior author attempted to detect the existence of a sensitivity toward hormones by experiments involving intracutaneous injections of the test substances. The results of this work were uncertain. Other authors have made similar experiments but failed to obtain convincing results. The indefinite outcome of these investigations can be ascribed to the fact that injections were made with aqueous extract of the hormones, in consequence of which, the period of contact between the allergen and the tissues was very limited. With most allergens, brief contact suffices to provoke a positive local reaction, but steroid hormones, not being easily soluble, require longer periods of action. We have found, however, that intracutaneous injection of steroid hormones in oil enables the allergen and tissue to remain in contact for the necessary length of time. On the other hand, the interpretation of allergic reactions following intracutaneous injection of hormones in oil is made difficult by the possibility that there is a hypersensitivity to the oily vehicle rather than to the hormone. Observations by other authors[4] of allergic reactions following the administration of steroid hormones in oil still left uncertainty as to whether the hormone or the oil was responsible for the production of allergy in these cases. In the experiments reported herewith we have succeeded in reducing the local reactions produced by intracutaneous injections of olive oil.

On first consideration, the existence in a patient of hypersensitivity to an endogenous steroid hormone may seem surprising, it being presumed that production of an allergic reaction requires the presence of a heterologous antigen. In the following, evidence is brought forward in support of the view that in certain conditions patients may react allergically to hormones produced by their own endocrine glands.

It is significant that allergic reactions are induced not only by the hormonal secretion (estradiol, testosterone) as such, but by products of hormonal metabolism excreted in the urine as well (estrone and androsterone). Among the steroid allergens two groups may be distinguished: (1) the hormones of the genital glands and their metabolites, and (2) the hormones of the adrenal glands. Several of the substances in question are known to be produced by both gonads and adrenals.

MATERIAL

In the present investigation, the following *crystalline* substances were tested:

1. Estradiol = hydrated pregnant urine estrogenic hormone.

2. Estrone = metabolite of *1*, excreted in the urine.
3. Progesterone = synthetic corpus luteum hormone.
4. Pregnandiol = synthetic metabolite of *3*.
5. Testosterone = synthetic testicular hormone.
6. Androsterone = synthetic metabolite of *5*.
7. Desoxycorticosterone acetate = synthetic adrenal cortex hormone.

Subjects not allergic to steroid hormones but sensitive to chorionic gonadotropin (prolan) and insulin were also encountered. Accordingly, all cases which reacted negatively to cutaneous injection with steroid hormones were tested with insulin (Boots) and korotrin (chorionic gonadotropin, Winthrop) in aqueous solutions.

INVESTIGATIONS ON THE ALLERGENIC PROPERTIES OF OLIVE OIL

The crystalline steroid hormones were dissolved by us and administered in olive oil solution. In view of the generally known allergenic properties of olive oil, control injections of the oil vehicle were always made along with the hormones. In addition, olive oil was studied separately as an allergen. A series of forty healthy, nonallergic women were given intracutaneous injections of 0.1 c.c. of pharmaceutic olive oil. The oil had been purified by neutralization with sodium carbonate and was desiccated with disodic sulfate and sodium chloride (according to *Pharmac. Helvetica VI*). Samples of the oil were then heated in an oven at 100° C. for 3, 24, 48, and 96 hours, respectively. Each of the forty normal women examined was tested with 0.1 c.c. of each of the four samples of heated oil simultaneously. The reactions were read 3 and 24 hours after injection. Positive cutaneous reactions to oil heated for 3 hours were observed in five cases (12.5 per cent), to oil heated for 24 hours in four cases (10 per cent), and to oil heated for 48 and 96 hours in three cases (7.5 per cent). The above observations prove that prolonged heating of the oil diminishes the number of allergic reactions following intracutaneous oil injection. The detection of subjects hypersensitive to oil was essential for this study, as all steroid hormones were given in olive oil solutions. Patients showing allergic reactions to olive oil should be eliminated from all further investigations in endocrine allergy, unless other vehicles are found, devoid of allergenic properties. It should be pointed out that in all the investigations reported in this paper, purified olive oil *Pharmac. Helvetica VI*) was used as the solvent for the crystalline steroid hormones.

TECHNIQUE

Cutaneous tests were performed on 182 women. The seven steroid hormones mentioned* were used in these tests in equal concentrations of 0.1 mg. per 0.1 c.c. of pure pharmaceutic olive oil. In control tests

*Pregnandiol, as an additional test allergen, was introduced toward the end of this investigation and was employed in only forty-two cases.

the olive oil vehicle was injected alone and, as a further means of control, tests were run with cholesterol (the mother substance of the steroid hormones) in corresponding concentration (0.1 mg. per 0.1 c.c.). It should be mentioned that in all cases of sensitivity to oil or cholesterol, the cutaneous reaction to all seven steroid hormones was positive. This occurred in seventeen cases (9.3 per cent). Of course, all oil- and cholesterol-sensitive cases were excluded from further investigations. The hormone and control solutions were given with a small needle, intradermally, on the volar side of the forearm in injections of 0.1 c.c. containing 0.1 mg. substance. As a routine procedure, the hormones of ovarian origin (estrone, estradiol, progesterone, pregnandiol) and cholesterol were injected in the right arm, and the adrocortical series (testosterone, androsterone, desoxycorticosterone acetate) and pure olive oil in the left arm. For every test a fresh syringe and needle were used to avoid reactions by contamination with different hormones. The results were read 3 to 5 and 24 hours after injection.

DETECTION OF SKIN SENSITIZING ANTIBODIES FOR HORMONES

A. *Positive Cutaneous Test.*—A reaction was considered positive when twenty-four hours after injection a red or rosy, slightly elevated papule of at least 0.5 cm. in diameter appeared at the site of injection. The papule disappeared when subjected to pressure and was accompanied by a sensation of itching. The reaction was also considered positive when a pink erythema of 2 to 3 cm. in diameter appeared twenty-four hours after injection accompanied by slight itching. Positive reactions usually persisted for forty-eight hours.

The diagnosis of endocrine allergy is established from the following: steroid hormones (0.1 mg.) were injected in 0.1 c.c. olive oil solution intracutaneously in the arm. The reaction is positive if it occurs within three to five hours or later, and persists for twenty-four hours or more after injection. A reaction which appears twenty-four to forty-eight hours after injection is also to be considered positive. If the reaction is positive within three to five hours and negative later, the recurrent test reaction should be carried out (Table I).

B. *Recurrent Test Reaction.*—In certain cases a "positive reaction" appeared three to five hours after injection, and disappeared some hours later. The significance of these reactions is doubtful, since prolonged contact between the tissue and the substance to be tested is necessary before a truely positive reaction can take place. In doubtful cases, a recurrent test reaction was performed as follows: Twenty-four hours after intracutaneous injection of 0.1 mg. of the test hormone, 1 mg. of it was injected *subcutaneously*. The test was considered positive when, three to five hours after the subcutaneous injection, a slight reddening accompanied by itching appeared at the site of the previous intradermal test. The production by subcutaneous hormone injection of a reaction at the site of a previous intracutaneous injection

TABLE I

EVALUATION OF ALLERGIC REACTION TO INTRACUTANEOUS INJECTION OF STEROID HORMONES

REACTION AFTER 3 TO 5 HOURS	REACTION AFTER 24 HOURS	RESULT
+	+	Positive
−	+	Positive
+	−	Doubtful, recurrent test reaction necessary
−	−	Negative

TABLE II

RECURRENT TEST REACTION IN NINETEEN PATIENTS

HORMONE TESTED	NUMBER OF POSITIVE REACTIONS
Estradiol	5
Estrone	6
Progesterone	4
Pregnandiol	1
Testosterone	2
Androsterone	−
Desoxycorticosterone acetate	1

is evidence of the existence of an allergic reaction toward the injected substance. This phenomenon was observed in nineteen cases (Table II).

C. *Retarded Test Reaction.*—In several cases, positive response to the intracutaneous test occurred at the site of injection many days after the injection, shortly before or with the appearance of premenstrual bleeding. In one case of sensitivity to estradiol, a positive skin test set in as late as eighteen days after the injection. In two other cases, one sensitive to estradiol and the other to desoxycorticosterone acetate, both tested intracutaneously, a positive reaction (itching and reddening) reappeared at the site of injection during each of the six successive premenstrual periods. This delay in appearance of the reaction suggests that in these cases an antibody against the hormonal allergen was formed when the sex hormone in the body was at its maximal level.

D. *Evaluation of Allergic Reactivity to Hormones.*—It is generally admitted that the degree of specific reactivity of the skin to an intracutaneously injected allergen is dependent in part upon the amount of active principle in the solution tested. In cases with a particularly strong local reaction, following the intracutaneous injections of 0.1 mg. of steroid hormone, the allergic reactivity was evaluated by testing with different dilutions of the hormonal allergen. In most cases the positive cutaneous reaction persisted even when 0.01 mg. of allergenic hormone was given instead of the usual dose of 0.1 milligram. In some instances quantities as small as 0.0001 mg. (0.1 γ) were sufficient to elicit a positive local reaction. It was noted that the size and intensity of the cutaneous reaction are related to the amount of the

hormonal allergen injected. In Fig. 1 different cutaneous reactions to various concentrations of estrone (0.001 to 0.1 mg.) in one estrone-sensitive woman may be seen. This method of testing was also important in the desensitization treatment, so as to avoid overstrong reactions and untoward symptoms due to excessive doses. The initial dose in desensitization was the minimal amount of hormone, able to bring about a positive cutaneous reaction.

Fig. 1.—Allergic sensitivity to estrone in various concentrations: *a*, 0.1 c.c.=0.1 mg. estrone, *b*, 0.1 c.c.=0.01 mg. estrone, *c*, 0.1 c.c.=0.001 mg. estrone, and *d*, 0.1 c.c. of olive oil (control).

E. *Insulin and Chorionic Gonadotropin in Cutaneous Tests.*—Insulin and korotrin* in aqueous solution were tested. Cutaneous reactions appeared, therefore, after a much shorter interval.

The insulin (Boots, 1 c.c. = 20 I.U.) was used in a 1:10,000 dilution; 0.1 c.c. of this dilution contained 0.0002 units of insulin. As a control, saline was employed.

Chorionic gonadotropin (korotrin, 1 amp. = 5,000 I.U.) was diluted to 1 unit per cubic centimeter with normal saline, and 0.1 c.c. of this

*We are indebted to the Winthrop Chemical Company, New York, for their kindness in supplying korotrin.

solution (0.1 unit of prolan) was given. Controls received the same prolan after it had been inactivated by boiling.

Reactions were rated positive if a large area of erythema with urticarial edema appeared within one to two hours following injection. Our experience with insulin and chorionic gonadotropin as allergens is still limited. We encountered one patient who was sensitive to insulin and could be desensitized, and also one case of sensitivity toward chorionic gonadotropin. It should be pointed out that allergy to insulin has already been reported by Lowell[5] who studied a patient allergic to both animal and human crystalline insulin.

F. *Intracutaneous Tests With Steroid Hormone Crystals.*—Intracutaneous tests with aqueous suspensions of finely crushed steroid hormone crystals were performed in three cases. Suspensions of estrone, estradiol, and progesterone containing 1 mg. of crystals in 1 c.c. of water were injected intracutaneously (0.1 c.c.) in women who had reacted strongly to one of these hormones in previous tests with oily solutions. Positive cutaneous reactions were observed in all three cases. These reactions appeared five to ten hours after injection and persisted for two to five hours. In one of the above cases, tested with a crystalline suspension of estradiol, the "retarded test reaction" was also observed. The positive reaction to estradiol reappeared spontaneously at the site of the previous injection of crystals during two successive premenstrual periods. These tests were not employed as a routine method for detecting endogenic allergic subjects because of the difficulty in handling the suspensions.

G. *Intracutaneous Tests With Estrone and Estradiol.*—Aqueous solutions of estrone and estradiol containing 0.01 mg. of hormone per 1 c.c. of water were also assayed by intracutaneous tests in women known to be sensitive to these substances. These tests were performed in five cases receiving 0.1 c.c., all of whom reacted positively. These reactions were of the immediate type, setting in ten to thirty minutes after injection and persisting for one-half to two hours. The transitory and inconstant character of the skin reactions with hormones in aqueous solution makes the use of this technique less suitable for diagnostic purposes than that in which an oily solution is employed.

H. *Tests With Insulin, Korotrin, and Steroid Hormones.*—Scratch and patch cutaneous tests with insulin, korotrin, and steroid hormones were performed in a series of cases. The reactions to insulin and korotrin as well as to steroid hormones were found to be uncertain and difficult to interpret and were hence of no value for clinical purposes.

DETERMINATION OF ALLERGIC ANTIBODIES IN SERUM OF PATIENTS SENSITIVE TO ENDOGENOUS HORMONES

An allergic reaction occurs when the allergen comes in contact with its specific antibody or reagin. The determination of the specific reagins circulating in the serum of patients sensitive to endogenous hormones is

necessary in order to demonstrate the existence of endocrine allergy. The following material furnishes evidence that:

1. The serum of patients allergic to endogenous hormones contains specific antibodies able to cause a positive passive transfer test (Prausnitz-Kuestner test).

Two series of ten normal women each received intracutaneous injections of 0.1 c.c. of serum from two estrone sensitive patients, one of whom had been suffering from hay fever, and the other from premenstrual migraine. Both samples of serum were taken at the height of complaints. As a control, these women received intracutaneous injections of serum from normal individuals. Twenty-four hours later 0.1 c.c. of an aqueous solution of estrone, containing 0.1 mg. per cubic centimeter, was injected intracutaneously at the site of the previous intracutaneous serum injection. The results were read thirty minutes to one hour after the injection of estrone. In eight cases of one series and seven of the other an erythema, accompanied by a wheal and sometimes by itching, appeared at the site of injection. No reaction was noted at the site of normal serum injections (Table III). These passive transfer reactions should be considered specific in view of the fact that all controls, as specified in Table III, were negative.

TABLE III

PASSIVE TRANSFER OF HYPERSENSITIVENESS WITH SERUM CONTAINING ANTIESTRONE REAGINS

SITE	FIRST INJECTION	SECOND INJECTION 24 HOURS LATER	RESULTS 30 MIN. TO 1 HOUR LATER
1	0.1 c.c. of serum A*	0.1 c.c. of estrone solution‡	+
2	0.1 c.c. of serum A	0.1 c.c. of normal saline	–
3	1.0 c.c. of serum B†	0.1 c.c. of estrone solution	–
4	0.1 c.c. of serum B	0.1 c.c. of normal saline	–
5		0.1 c.c. of estrone solution	–
6		0.1 c.c. of normal saline	–

*Serum A=serum of a patient suffering from intermittent migraine and hypersensitive to estrone (drawn during the attack).

†Serum B=serum of normal women.

‡Estrone solution=0.1 mg. of estrone dissolved in 1 c.c. of one hundredth-normal sodium hydroxide.

2. Intracutaneous injections of such serum may, under certain conditions, elicit spontaneous, positive, cutaneous reactions, without subsequent injection of the allergen at the same site; this happens when the concentration of the hormonal allergen in the body of the normal subject is at a high level: either when the hormonal content of the body is at its physiologic peak, or after injections of allergenic hormones. This positive spontaneous response to injections of serum from hormone-sensitive patients containing reagins to hormones was named "spontaneous passive transfer test."

Here, it was noted that the serum of patients sensitive to endogenous hormones induced spontaneous positive cutaneous reactions in normal

women, without the subsequent introduction of the hormonal allergen. This phenomenon takes place as a result of sufficiently high concentrations of the allergenic hormone in the body of the normal individual tested. Serum, 0.1 c.c., from an estrone-sensitive woman suffering from premenstrual migraine, drawn during the attack, was given intracutaneously to a normally menstruating woman shortly before menstruation. Twenty-four hours later an erythematous reaction accompanied by itching appeared at the site of injection. No reaction was observed with 0.1 c.c. of serum from a normal individual, injected into the patient tested. The serum of the estrone-sensitive woman when heated at 56° C. for one-half hour gave a smaller reaction, and when heated at 37° C. for twenty-four hours gave no reaction. When all the tests, described above, were repeated in the same women shortly after menstruation, no positive response to the serum injections was noted. This fact suggests that spontaneous reactions with serum containing antiestrone reagins may occur on the skin of a normally menstruating woman, when the concentration of the hormonal allergen (estrogens) in the body reaches its maximal value (in the premenstrual phase). This was also confirmed by the fact that the same women reacted positively even after menstruation when 5 mg. of estrone or estradiol benzoate were given intramuscularly twelve hours prior to the intracutaneous reagin-containing serum injection (Table IV). A series of similar tests was also performed in three women after menopause. These latter did not give a spontaneous response to the serum of estrone-sensitive women; on the other hand, when the same tests were made fol-

TABLE IV

SPONTANEOUS PASSIVE TRANSFER TEST WITH SERUM CONTAINING ANTIESTRONE REAGINS

SITE	SEXUAL PHASE	INJECTION	RESULTS 24 HOURS LATER
1	Premenstrual phase	0.1 c.c. of serum A*	+
2	Premenstrual phase	0.1 c.c. of serum A heated at 56° C. for 30 minutes	±
3	Premenstrual phase	0.1 c.c. of serum A heated at 37° C. for 24 hours	–
4	Premenstrual phase	0.1 c.c. of serum B†	–
5	Postmenstrual phase	0.1 c.c. of serum A	–
6	Postmenstrual phase after injection of 5 mg. estrone	0.1 c.c. of serum A	+
7	Postmenstrual phase after injection of 5 mg. estrone	0.1 c.c. of serum B	–
8	Climacterium	0.1 c.c. of serum A	–
9	Climacterium after injection of 5 mg. estrone	0.1 c.c. of serum A	+
10	Climacterium after injection of 5 mg. estrone	0.1 c.c. of Serum B	–

*Serum A=serum of a patient suffering from intermittent migraine and hypersensitive to estrone (drawn during the attack).

†Serum B=serum of normal women.

lowing an injection of 5 mg. of estrone or estradiol benzoate a positive response was obtained in two of the three women tested.

3. The properties of reagins induced by hormonal allergens have been identified as similar to those of allergic reagins in general. They are the following:

a. The passive sensitizing property of antiestrone reagins contained in serum was lessened by heating for one-half hour at 56° C. and destroyed by heating at 37° C. for twenty-four hours.

b. No visible precipitation occurs when the serum is mixed with its specific antigen, estrone.

c. No complement fixation antibodies to estrone were found in the serum of estrone-sensitive women.

d. No anaphylactic response to estrone was found in the guinea pig experiment either in vivo or in vitro (Schultz-Dale test).

The above properties are accepted as characteristic of reagins in the serum of allergic patients.[6]

GENERAL ALLERGIC REACTIONS FOLLOWING HORMONAL CUTANEOUS TESTS

Of 165 women who underwent cutaneous tests (after exclusion of seventeen oil-sensitive cases), four reacted with serious general disturbances as well as positive local reactions. Although the dose of hormone used, 0.1 mg., was too small to elicit direct hormonal or toxic effects, the general reaction was quite severe. It consisted of vomiting, urticaria, dizziness, fever, metrorrhagia, etc. The four cases reported are summarized here.

CASE REPORTS

CASE 1.—H. D., aged 43 years, consulted us for pruritus vulvae which appeared periodically, particularly one week prior to menstruation and ceased at the onset of menstruation. She complained of premenstrual tension. No allergic manifestations were reported in family or personal history. Blood eosinophilia was 7 per cent. The cutaneous test for estrone, twenty-four hours after injection, was positive and accompanied by severe generalized urticaria with itching and a slight febrile reaction. These symptoms subsided after forty-eight hours' duration.

CASE 2.—A. L., aged 35 years, complained of migraine which occurred for ten years at the fourteenth and twenty-sixth day of the menstrual cycle. There were no allergic antecedents in family or personal history. Blood eosinophilia was 6 per cent. There was no previous hormonal treatment. A positive cutaneous test for estrone appeared after twenty-four hours; at the same time she complained of general disturbances: fever 39.5° C., nausea, vomiting, migraine, diarrhea, and metrorrhagia. These symptoms subsided after twenty-four hours.

CASE 3.—P. G., aged 15 years, consulted us for facial acne which increased premenstrually. Numerous allergic manifestations appeared in

the family history. No eosinophilia was present. No previous hormonal treatment was taken. A hormone injection test revealed sensitivity to progesterone. Six hours after injection, nausea and abundant vomiting set in, followed by high fever (40° C.). At the same time exacerbation of the facial acne and abundant metrorrhagia occurred. These disorders lasted for twenty-four hours.

CASE 4.—E. C., aged 57 years, complained of persistent pruritus vulvae for five years. Various complaints of allergic nature—asthma and migraine—were elicited. Blood eosinophilia was 8 per cent; blood sugar, 84 mg. per cent. Pruritus vulvae as well as the other allergic manifestations became more severe after the ingestion of sugar. It seems possible that the ingestion of sugar provokes exaggerated secretion of insulin which acts as the allergen. The cutaneous test with 0.0002 I.U. of insulin was positive. On the day of injection the patient suffered an attack of dyspnea and aggravation of her pruritus vulvae, accompanied by general weakness, nausea, and anorexia.

Of the cases mentioned, three had not received previous hormonal treatment. The sensitization of these patients, therefore, could have been brought about only by endogenous hormonal products acting as allergens. The women were subsequently treated with a progressively increasing dose of the allergenic hormone in question, and were thus desensitized.

CLINICAL CONFIRMATION OF THE EXISTENCE OF ENDOCRINE ALLERGIC CONDITIONS*

Intracutaneous tests with various hormones were performed on 165 women (Table V). The family and personal allergic histories of these women were taken, and their blood was studied for eosinophilia. The patients may be divided into eight groups (Table V).

Group A.—Normal women: This group included thirty-two healthy, normally menstruating women. The hormonal cutaneous tests were performed in this group at various stages of the menstrual cycle. *In all these cases the tests were negative.* Two of the women were subjected to estrone and progesterone tests at three-day intervals during the menstrual cycle, but at no time did they show any cutaneous reaction. These negative findings demonstrate that the cycle, with its various hormonal phases, does not influence the skin reaction.

Group B.—This group included women suffering from diseases, known or suspected to be of allergic nature, the symptoms appeared or were aggravated in relation to menstruation. The patients in this series complained of the following disorders: asthma, vasomotor rhinitis, angioneurotic edema, chronic urticaria, certain eczemas, migraine, psoriasis and certain ophthalmologic conditions. This series of twenty-seven

*In this report clinical data will be reported only in so far as is necessary to support the existence of endocrine allergic conditions. Detailed clinical observations will be reported in a subsequent paper.

women showed a high percentage of positive cutaneous tests (19 = 70 per cent), frequent occurrence of allergic manifestations in personal and family histories and high blood eosinophilia. Two cases of keratitis of unknown origin with sensitivity to desoxycorticosterone acetate* are included. These conditions were severely aggravated regularly before menstruation and could be cured by a desensitizing treatment with desoxycorticosterone acetate. One case of vasomotor rhinitis and two cases of asthma also responded favorably to desensitization with estradiol, estrone, and desoxycorticosterone acetate respectively.

Group C.—Ten cases of pruritus vulvae and eight cases of acne, related to or aggravated by menstruation, have been grouped in this category. Like the former group they showed frequent occurrence of positive cutaneous tests to hormone (13 = 72 per cent), as well as a high incidence of family and personal allergic history.

Group D.—Premenstrual tension: Among these cases were thirty-two women whose disorders generally consisted of pains in the lower abdomen and the back, nausea, vomiting, headache, and fever, beginning in the last week prior to menstruation and ceasing with the onset of bleeding. The high frequency of positive cutaneous tests (24 = 75 per cent) in this group of disorders justifies their incorporation into the group of "endocrine allergic diseases." Desensitizing treatment with increasing doses of allergenic hormones gave encouraging results in these cases. Premenstrual pains are distinct from menstrual pains (dysmenorrhea), because the latter cases failed to respond to cutaneous tests. This fact deserves special attention since it allows a conclusion as to the etiology of the two disturbances. If it is true that premenstrual dysmenorrhea is connected with endocrine allergy, and in this respect differs from menstrual dysmenorrhea, the existence of a fundamental difference in the genesis of these two conditions must be regarded as probable.

Group E.—Dysmenorrhea: In eleven cases of strong pains during menstruation (pain and psychic disorders *during* menstruation) the cutaneous response to the various tests was negative (0 per cent).

Group F.—Allergic diseases related to menopause: Thirteen cases of various allergic diseases which set in with the appearance of menopause were studied: asthma, 3; chronic urticaria, 3; chronic eczema, 2; and migraine, 5. Six of them (46 per cent) reacted positively to the hormonal cutaneous test. Of these, five had a previous history of allergic manifestations, and four had high blood eosinophilia.

Group G.—Pruritus vulvae related to menopause was studied in six cases, in four of which sensitivity to hormones (2 estrone, 1 prolan, 1 insulin) was observed.

Group H.—In *Groups B, C, F,* and *G* various conditions strictly related to hormonal metabolism were studied. The high percentage of positive cutaneous tests in these cases indicates that these disorders are

*We are under obligation to Prof. A. Feigenbaum and Dr. Miterstein who referred these cases to our Department.

TABLE V

OCCURRENCE OF POSITIVE SKIN TESTS IN 165 FEMALE PATIENTS

DIAGNOSIS	NUMBER OF CASES	CASES WITH POSITIVE CUTANEOUS TESTS	CASES WITH HIGH EOSINOPHILIA	CASES WITH ALLERGIC HISTORY
A. Normal women	32	–	–	–
B. Allergic diseases related to menstruation	27	19	11	16
C. Pruritus vulvae and acne related to, or aggravated by, menstruation	18	13	8	8
D. Premenstrual tension	32	24	10	9
E. Dysmenorrhea during menstruation	11	–	1	–
F. Allergic diseases related to menopause	13	6	4	5
G. Pruritus vulvae related to menopause	6	4	3	2
H. Diseases of *Groups B, C, F,* and *G,* not related to menstruation or menopause	26	2	8	10

due to allergy toward hormonal secretions. Their allergic character is also confirmed by the frequent family and personal allergic history and high blood eosinophilia. Conditions similar to those in *Groups B, C, F,* and *G* but not related to hormonal metabolism have been studied and are reviewed as a separate group. This group included: 5 cases of asthma, 6 cases of chronic urticaria, 2 cases of psoriasis, 5 cases of pruritus vulvae, 3 cases of acne, and 5 cases of migraine. In all these cases which were not dependent on the cyclic disturbances or menopause, only 2 (7 per cent) positive cutaneous tests (one in a case of chronic migraine, and one in a case of psoriasis) were recorded.

It should be emphasized, however, that allergic hypersensitivity to endogenous hormones is a rare condition, generally encountered only in relation to menstruation or menopause in allergic subjects. The frequent occurrence in our series of positive cutaneous tests to hormones (70 per cent in certain groups of disorders) is mainly due to the fact that *our cases were specially selected* and given the tests only when allergy to endogenous hormones was suspected. It is significant that cutaneous reactions were negative in all cases of healthy women, and in women suffering from dysmenorrhea. Positive reactions occurred almost exclusively in patients with definite clinical disturbances and then only when these were related to menstruation or menopause (Table V).

THERAPEUTIC RESULTS OF DESENSITIZATION

Desensitizing treatment was given in forty-four cases of sensitivity to various hormones. In twenty-two of the treated cases, all pathologic symptoms disappeared. In thirteen cases, marked improvement followed treatment; in the nine remaining cases, no amelioration was noted (Table VI).

TABLE VI

CLINICAL RESULTS OF DESENSITIZATION WITH HORMONES IN FORTY-FOUR FEMALE PATIENTS

HORMONAL SENSITIVITY TOWARD	NUMBER OF CASES TREATED	RECOVERED	IMPROVED	NO RESULT
Estrone	17	7	6	4
Estradiol	6	4	1	1
Progesterone	6	2	2	2
Testosterone	7	4	2	1
Desoxycorticosterone acetate	7	4	2	1
Insulin	1	1	-	-

Desensitization was accomplished by the administration of progressively increasing doses of the various allergenic hormones. The methods employed will be reported later in detail together with the clinical findings. The favorable results obtained by hormonal desensitization furnish further confirmation of the existence of endocrine sensitivity.

THE MECHANISM OF ENDOCRINE ALLERGY

Is endocrine allergy due to a quantitative change in the hormonal level of the body? Certain observations stand out against this possibility; viz., the hormonal cutaneous tests were negative both in (a) diseases involving reduced hormonal production (primary and secondary amenorrhea), and (b) diseases of increased hormonal secretion (hyperhormonal amenorrhea and bleeding). Negative results were obtained, moreover, in pregnancy, a condition in which production of estrogenic and gonadotropic hormones is enormously increased. The tests also gave negative results in our cases of toxemia of pregnancy (hyperemesis and dermatosis) where the production of hormones is even greater than in normal pregnancy. The fact that certain allergic diseases frequently show improvement during pregnancy finds an explanation in the assumption that the gradual increase of the hormonal level of the body during pregnancy brings about hormonal desensitization.

On the other hand, several facts must be considered which strengthen the view that hormonal allergy is correlated with increased hormone production in the organism. (a) The allergic manifestation (urticaria, asthma, etc.) frequently occurs during the premenstrual phase, i.e., when secretion of the estrogenic and corpus luteum hormones attains peak values. (b) Very often positive tests occur in women suffering from premenstrual disorders (premenstrual tension and dysmenorrhea, vomiting, cephalgia, etc.). (c) Positive tests often occur in early climacterium, a phase in which production of estrogenic hormone is known to be increased. (d) Retarded test reactions almost always occur during the premenstrual phase.

In spite of this, we are inclined to believe that endocrine allergic disturbances are not conditioned by an overproduction of hormones. It seems likely that some general constitutional factor is responsible for the observed sensitivity to endogenous hormones.

DISCUSSION

The existence of allergy to endogenously produced hormones may explain the pathogenesis of various gynecologic conditions. Thus, clinical pictures such as pruritus vulvae and various premenstrual disorders may, in part, be ascribed to allergic hypersensitivity to *different* endogenous hormones. This problem will be dealt with in a second paper.

It should be pointed out that Riebel[7] reported a case of premenstrual rhinitis in a woman hypersensitive to estrone. An injection of this hormone during the postmenstrual phase induced an attack in the patient.

Fintch[8] observed that pregnant women suffering from hyperemesis reacted with a wheal to progesterone when injected intracutaneously and the vomiting was improved by desensitization with progesterone. This result could not be confirmed by us in a series of four patients tested.

Urbach[9] assumed that in the study of allergy to endogenous hormones, special significance should be attributed to antihormones. According to this author, the presence of antihormones in the serum of certain normal, previously untreated human beings, points to the possibility that in pathologic conditions the organism might also produce allergic antibodies to endogenous hormones. This conception may be applied to sensitivity toward pituitary hormones and other proteide hormones since Zondek and Sulman[10] have brought evidence that the so-called antihormones evoked by them belong to the group of immune bodies. However, to the steroid hormones these considerations cannot be applied, since this group of hormones never forms antihormones.

Various nongynecologic disorders known to be conditioned by an allergic pathogenesis, which appear or are aggravated in relation to menstruation or menopause, may belong to the group of endocrine allergic diseases. Certain cases of asthma, vasomotor rhinitis, angioneurotic edema, and urticaria related to hormonal metabolism were also found to be due to hypersensitivity to the secretions of endocrine glands, or to their metabolites.

SUMMARY

1. It has been shown that certain pathologic manifestations are correlated with sensitivity toward endogenous hormones. They have been designated, therefore, as conditions of "endocrine allergy."

2. In certain pathologic conditions, related to the menstrual cycle or the appearance of menopause, skin reagins to the steroid hormones—estrone, estradiol, progesterone, pregnandiol, testosterone, androsterone, or desoxycorticosterone acetate—can be demonstrated in the patient by active cutaneous tests. Analogous conditions of sensitivity to insulin and prolan may occur.

3. Allergic endocrine hypersensitiveness may also be demonstrated by the "recurrent test," i.e., by the appearance of a local reaction at the site of a first intracutaneous test, following a *subcutaneous* injection twenty-four hours later of the allergenic hormone at a new site.

4. When the cutaneous reaction in cases of endocrine allergy is delayed, it often occurs in the premenstruum, viz., at a time coincident with the attainment of maximum level in the body by the allergenic hormone in question ("retarded test reaction").

5. Normal subjects injected intracutaneously with serum of patients hypersensitive to estrone yielded positive cutaneous reactions when a solution of estrone was given subsequently at the site of the former serum injection (positive Prausnitz-Kuestner test). Serum of patients hypersensitive to estrone may also cause positive cutaneous reactions following its intracutaneous injection into normal subjects; this occurs when the concentration of hormonal allergen in the body of the normal subject reaches high values (either physiologically or following injection).

6. The properties of reagins induced by hormonal allergens have been identified as similar to those of allergic reagins in general.

7. The degree of specific reactivity of the skin, to hormonal allergens injected intracutaneously, is related to the amount of the active principle in the solution tested.

8. Injections of minimal quantities of steroid hormones in oily vehicle, into persons who have not previously received hormone treatment, may cause serious general symptoms.

9. Personal and family histories of allergy and high blood eosinophilia are frequent in persons with positive cutaneous tests.

10. Favorable clinical results, obtained by desensitization, furnish a further proof that the disturbances in question are caused by endocrine allergy.

11. Allergy to endogenous hormones has been observed in women suffering from disorders related to menstruation or menopause, but never in healthy subjects.

12. The results of our investigations lead us to assume that certain gynecologic conditions like pruritus vulvae, and various premenstrual disorders are conditioned by allergy to endogenous hormones. This is also true for disturbances, known to be of allergic nature (asthma, vasomotor rhinitis, angioneurotic edema, and urticaria) related to menstruation or menopause.

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BLOOD STUDIES IN ALLERGY

III. Cellular Reactions in Sulfonamide Sensitivity*

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THE blood response following the trial ingestion of a sulfonamide drug has been studied in three cases of known sulfonamide sensitivity. Total and differential leucocyte counts were made prior to and at frequent intervals for as long as as ten days following the oral administration of a test dose.

A white blood cell diluting fluid consisting of phloxine and methylene blue dissolved in equal parts propylene glycol and water[1-3] was employed. This technique permits the counting chamber differentiation of eosinophiles, polymorphonuclear and mononuclear leucocytes, in the same specimen upon which the total leucocyte count is determined. Differential counts of 100 cells in the counting chamber and 200 cells from the Wright stained film were made at each observation.

The total number of eosinophiles was determined by counting the eosin staining cells in the ruled area of one side of the counting chamber (i.e., in 9 squares multiplied by 22.2 to obtain the number per centimeter of blood) and as a result of the differential count of 100 cells in the chamber and 200 cells of the stained film. There is reason to believe that the counting chamber technique affords a more accurate method of enumerating eosinophiles than that obtained from the differential count of the stained film.[4] Records of the temperature, pulse, and blood pressure were secured at each observation; in two of the cases vital capacity determinations were also made.

CASE REPORTS

Case 1.—A. A., a graduate nurse, aged 55 years, had been subject to intermittent attacks of rhinitis and nasal obstruction since 1925, recurrent right maxillary sinus infection since 1928, and bronchial asthma since 1938. The typical and frequently repeated course of events in recent years which had started with an allergic rhinitis, was followed within a few days by infection of the right antrum and asthma. Various types of treatment, including a submucous resection, nasal polypectomy, dust avoidance, dietary management, autogenous vaccine, and foreign protein therapy had failed to relieve her symptoms.

Because her acute attacks of asthma were usually preceded by a "cold" and sinus infection, it was assumed that an infection was the cause of her asthma, and several episodes were treated with sulfonamide drugs. With further observation it became evident that her acute

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symptoms had corresponded to the grass or ragweed pollen seasons or had been associated with house dust exposure, although she consistently showed negative cutaneous and intracutaneous skin reactions to these as well as to all other test antigens. Specific pollen hyposensitization during the 1943 seasons produced marked relief and avoided the complicating sinus infection previously present at that time of the year. Dust hyposensitization since November, 1943, has resulted in a definite diminution in her winter rhinitis and asthma.

Her first sulfonamide therapy was received Jan. 20, 1942, at the time of a purulent sinus infection associated with bronchial asthma. Sulfadiazine, 3 Gm., was taken daily for a week without an appreciable change in her sinus infection or asthma. Sulfathiazole, 3 Gm. daily, was started immediately following and continued in this dose for three weeks. Her symptoms subsided during the third week.

The second course of sulfathiazole, 3 Gm. daily, was prescribed under similar circumstances in June, 1942. By the end of the second day there was improvement in the sinus infection and asthma. The drug was continued for a week; at the end of this time she was symptom free, and there had been no variation from normal in the total leucocyte count.

Another bout of rhinitis developed in mid-August, 1942, followed by pain in the right maxillary sinus region on August 22, and asthma on August 31. Sulfathiazole, 3 Gm. daily, was started September 1. On the third day (after 9 Gm. of the drug) the total white cell count dropped to 3,200 cells per cubic millimeter, and the drug was immediately stopped. There were apparently no symptoms related to the medication. The rhinitis and asthma continued for another three weeks.

She returned Dec. 20, 1942, with a recurrence of symptoms and requested another trial of sulfathiazole. The note regarding her previous neutropenia had been misfiled in her record and this fact was not appreciated as the drug was prescribed for the fourth time, 1 Gm., being given at 5:00 P.M. Lassitude and malaise developed two hours later and were followed by chills and a progressive temperature elevation. Upon admission to the hospital at 10:15 P.M. she complained of nausea, severe headache, and generalized aching. The admission white blood count was 2,800. The temperature reached a maximum of 102.4° F. By morning the leucocyte count was 5,300, and all symptoms had subsided except for residual fatigue. It is of interest that there was a distinct improvement in the rhinitis and asthma for a week following this reaction. The latter then gradually returned in its former severity.

On October 2, 1943, she volunteered to take 1 Gm. of sulfathiazole. The clinical observations and blood counts are recorded in Table I. Cellular changes in absolute values are represented graphically in Charts 1 and 2.

From a fasting pre-ingestion level of 8,800 cells per cubic millimeter the white count fell to 3,550 at the end of the first hour and reached a

TABLE I

CASE I. (A. A.) THE BLOOD RESPONSE AND SYMPTOMS

TABLE I

CASE 1. (A. A.) THE BLOOD RESPONSE AND SYMPTOMS FOLLOWING THE INGESTION OF 1 GM. OF SULFATHIAZOLE

DATE	TOTAL WHITE COUNT	DIFFERENTIAL WHITE CELL COUNTS												SYMPTOMS
		COUNTING CHAMBER				STAINED FILM								
		EOSINOPHILES (9 SQUARES)	POLYMORPHONUCLEARS	MONONUCLEARS	EOSINOPHILES	POLYMORPHONUCLEARS	STABS	METAMYELOCYTES	PROMYELOCYTES	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	MONOCYTES	
9/27 9:00 A.M.	10,750	7.4	65	30	5	40.0	7.0	0.0	0.0	11.0	0.5	38.5	3.0	Moderately severe bronchial asthma
9/28 9:00 A.M.	9,950	11.3	51	36	13	38.0	7.0	0.0	0.0	13.5	1.5	36.5	3.5	
9/29 9:00 A.M.	10,900	5.3	48	48	4	48.0	14.0	0.0	0.0	7.5	1.0	20.0	9.5	Mild bronchial asthma
9/30 9:00 A.M.	7,250	7.9	51	39	10	38.5	16.0	0.0	0.0	10.0	2.0	30.5	3.0	
10/1 9:00 A.M.	10,200	7.1	46	49	5	23.5	10.0	0.0	0.0	5.0	1.0	57.0	3.5	Mild bronchial asthma
10/2 12:45 P.M.	9,950	6.9	46	46	8	44.0	10.0	0.0	0.0	10.0	0.5	30.5	5.0	
12:58 P.M.	8,800	7.4	41	54	5									Mild bronchial asthma
1:00 P.M.		*1 Gm. sulfathiazole administered orally*												
1:30 P.M.	7,600	7.3	49	42	9									
2:00 P.M.	3,550	8.5	51	40	9	40.0	9.5	0.5	0.0	7.5	0.5	41.0	1.0	Chilliness, frontal headache
2:30 P.M.	3,360	4.0	37	57	6									
3:00 P.M.	2,650	0.8	40	59	1	36.0	15.5	0.0	0.0	0.0	0.0	48.5	0.0	Malaise, generalized aching
3:30 P.M.	5,200	0.0	59	41	0									
4:00 P.M.	5,150	0.4	44	56	0	16.5	36.0	6.0	1.5	0.5	0.5	39.0	0.0	Chills, rhinorrhea, nausea
5:00 P.M.	4,250	1.0	63	36	1	19.5	44.0	7.5	0.5	1.5	0.0	27.0	0.0	Vomiting, diarrhea
6:00 P.M.	5,850	1.1	70	28	2	26.5	64.0	2.0	0.0	1.5	0.0	6.0	0.0	Chills, nausea, diarrhea
7:00 P.M.	7,850	0.8	82	17	1	31.0	63.0	3.0	0.0	0.0	1.0	2.0	0.0	Severe backache
8:00 P.M.	12,250	0.3	89	10	1	19.5	71.0	3.5	1.5	0.5	0.5	3.0	0.5	Drowsy, extremely fatigued
9:00 P.M.	12,200	0.0	93	7	0	33.5	56.0	4.0	0.0	0.5	0.5	5.5	0.0	Generalized soreness
10:00 P.M.	12,700	0.0	93	7	0	35.5	58.5	2.5	2.0	0.0	0.0	1.5	0.0	Residual fatigue, weakness
11:00 P.M.	13,000	0.2	95	5	0	52.5	37.5	1.5	3.5	0.0	0.0	3.0	2.0	Residual fatigue, weakness
10/3 8:00 A.M.	19,600	0.0	92	8	0	49.0	38.0	4.0	2.5	0.0	0.0	6.5	0.0	Residual fatigue, weakness
12:00 N.	18,250	0.1	91	9	0	49.5	38.0	2.0	1.0	0.0	0.0	8.0	1.5	Residual fatigue, weakness
5:00 P.M.	13,800	0.5	85	14	1	45.5	41.0	1.5	1.5	0.5	0.0	9.5	0.5	Moderate fatigue, weakness
9:00 P.M.	16,000	4.0	74	24	2	51.5	30.0	2.0	1.5	1.0	1.5	12.0	0.5	Moderate fatigue, weakness
10/4 9:00 A.M.	14,050	4.5	69	26	5	47.0	24.0	3.5	0.5	6.5	0.0	17.0	1.5	Moderate fatigue, weakness
12:00 N.	11,300	3.5	71	28	1	48.5	23.0	2.0	0.0	3.5	0.5	18.5	4.0	Moderate fatigue, weakness
10/5 9:00 A.M.	9,400	5.6	47	51	2	45.0	10.5	2.5	0.0	4.0	0.5	36.0	1.5	Slight fatigue, weakness
5:00 P.M.	10,450	3.2	45	52	3	50.0	10.0	2.0	0.0	3.5	0.0	34.0	0.5	Slight fatigue, weakness
10/6 9:00 A.M.	8,950	9.0	40	44	16	40.0	6.0	2.5	0.0	7.5	0.5	43.0	0.5	Ease of fatigue
10/7 9:00 A.M.	7,350	5.0	39	56	5	41.0	8.0	2.0	0.0	8.5	0.0	40.0	0.5	Ease of fatigue
10/8 9:00 A.M.	9,700	4.0	38	58	4	43.5	7.5	1.5	0.0	5.5	1.5	40.0	0.5	
10/10 9:00 A.M.	10,650	2.0	56	42	2	52.0	10.0	0.5	0.0	2.5	0.0	34.0	1.0	

low of 2,650 two hours after ingestion and remained depressed for four hours. The latter period was characterized by a progressive increase in the young myeloid cells which presaged and continued into the period of leucocytosis beginning at seven hours. The elevation of the total leucocyte count from a minimum of 2,650 at two hours to 12,250 at seven hours appeared to be the direct result of the increase in the number of young myeloid cells (Chart 1). These cells, principally "stab"

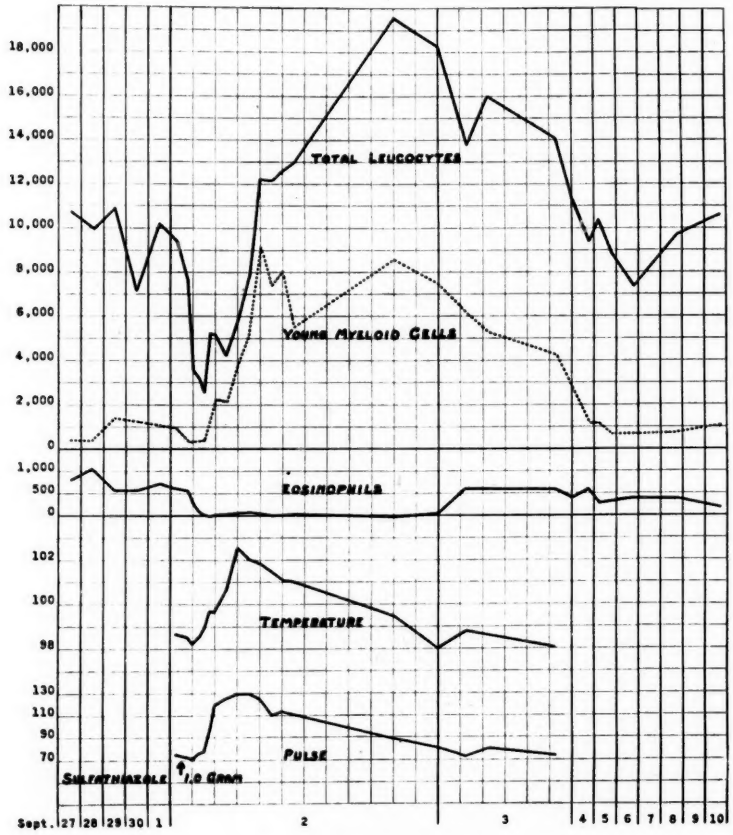

Chart 1.—Case 1. (A. A.) The cellular response and clinical observations following the ingestion of 1 Gm. of sulfathiazole.

forms, included a small number of less mature forms, but no myeloblasts were observed. The fact that cells of the myeloid series were responsible for the delayed leucocytosis, reaching a maximum of 19,600 at seventeen hours, is evident from a comparison of the total leucocyte curve of Chart 1 and the similar contours of the differential counts shown graphically in Chart 2.

An absolute diminution in lymphocytes developed shortly after the granulocytes began to shift to the left and increase in number. Lymphopenia, reaching a minimum of 157 cells per cubic centimeter at six

hours, continued for the following four hours; a relative diminution in lymphocytes persisted for two days. These changes are also illustrated in Chart 2.

A reduction of the eosinophiles was noted at one and one-half hours; one hour later they had disappeared from the peripheral circulation (i.e., no eosinophiles were observed in the entire ruled and unruled areas of the two sides of the counting chamber). They remained depressed for twenty-four hours, a period corresponding to the elevations of the temperature and pulse. The blood pressure did not show a significant or constant change.

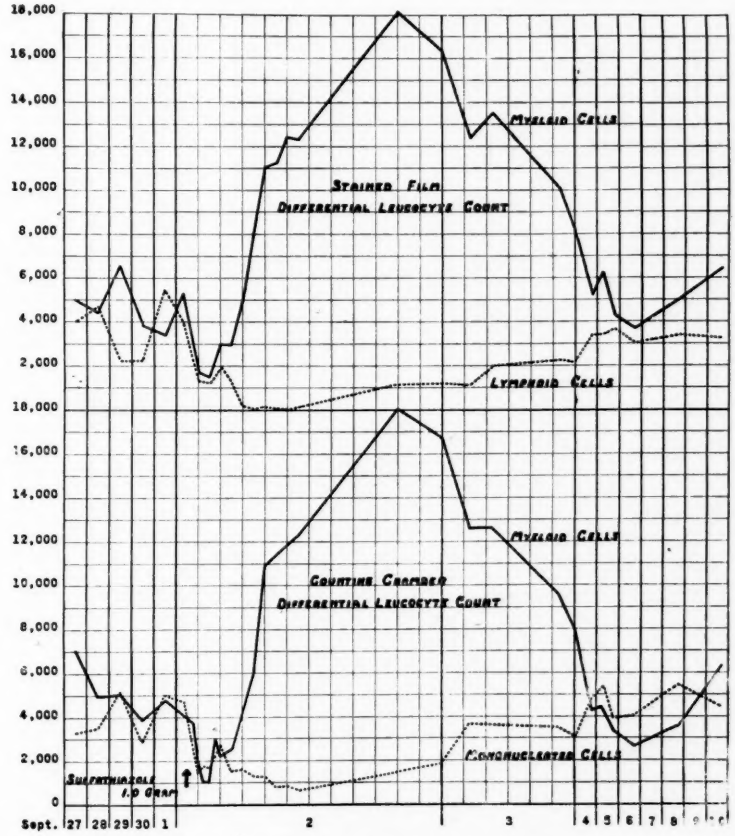

Chart 2.—Case 1. (A. A.) Comparison of the differential counts by the stained film and counting chamber techniques following the ingestion of 1 Gm. of sulfathiazole.

Two additional cases were studied from this viewpoint incidental to observations in evaluating the significance of bronchial asthma developing during sulfonamide therapy. Detailed histories of these cases have been presented elsewhere.[5]

Case 2.—F. F., male, aged 40 years, with a negative past and family history of allergic disease, developed his initial attack of bronchial

TABLE II

CASE 2. (F. F.) THE BLOOD RESPONSE AND SYMPTOMS FOLLOWING THE INGESTION OF 2 GM. SULFATHIAZOLE

DATE	TOTAL WHITE COUNT	DIFFERENTIAL WHITE CELL COUNTS												REMARKS
		COUNTING CHAMBER				STAINED FILM								
		EOSINOPHILES (9 SQUARES)	POLYMORPHONUCLEARS	MONONUCLEARS	EOSINOPHILES	POLYMORPHONUCLEARS	STABS	METAMYELOCYTES	PROMYELOCYTES	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	MONOCYTES	
10/4 9:00 A.M.	7,700	7.2	57	35	8	51.5	7.5	0	0	16.5	1.0	23.0	0.5	Chest examination negative
10/5 8:15 A.M.	8,750	10.6	54	39	7	50.5	11.5	1.5	0	14.0	0	20.5	2.0	Chest examination negative
8:30 A.M.	8,750	11.8	55	37	8	45.0	11.5	0.5	0	16.0	1.0	25.0	1.0	Chest examination negative
9:00 A.M.	*2 Gm. sulfathiazole administered orally*													
9:30 A.M.	6,400	11.4	60	31	9	44.5	13.5	3.0	0.5	8.0	0.5	29.0	1.0	Chest examination negative
10:00 A.M.	7,850	13.2	62	22	16	48.0	10.5	2.0	0	9.5	1.0	27.0	2.0	Chest examination negative
10:30 A.M.	7,600	7.3	56	36	8	46.0	11.5	2.5	0.5	9.5	1.0	28.0	1.0	Coughing after vital capacity
11:00 A.M.	7,450	7.3	68	23	9	48.5	12.5	4.0	0	6.0	0	28.0	1.0	Coughing, drowsiness
11:30 A.M.	6,900	5.7	64	32	4	45.5	13.0	5.0	0.5	6.5	1.0	27.5	1.0	Coughing, heavy chest
12:00 N.	7,700	5.2	63	30	7	47.5	12.5	2.5	0.5	8.5	2.0	26.5	0	Coughing, chest examination negative
1:00 P.M.	7,950	4.0	65	31	4	58.5	21.0	3.5	1.0	4.0	0	12.0	0	Dyspneic, râles in chest
2:00 P.M.	7,400	7.5	70	23	7	53.5	12.5	2.0	0.5	11.0	0.5	18.5	1.5	Moderately severe asthma
3:00 P.M.	7,950	5.0	64	30	6	48.0	19.5	1.5	0.5	4.5	0.5	25.0	0.5	Moderately severe asthma
4:00 P.M.	*First food taken during day*													Slight cyanosis
4:30 P.M.	9,950	5.5	72	22	6	49.5	16.0	1.5	0.0	8.5	0.5	23.0	1.0	Wheezing less, cough productive
7:30 P.M.	9,600	9.0	60	30	10	64.0	23.0	2.0	0	4.0	0.0	7.0	0.0	Wheezing less, cough productive
11:00 P.M.	11,400	13.3	66	20	14	57.5	12.5	1.5	0	8.0	0	19.0	1.5	Râles only after vital capacity
10/6 3:00 A.M.	10,900	13.2	59	26	15	50.0	10.0	2.5	0	17.0	1.0	17.5	2.0	Moderately severe asthma*
8.00 A.M.	10,000	23.0	50	30	20	34.0	11.5	3.0	0	33.5	1.0	15.0	2.0	Mild asthma
10:30 A.M.	9,500	20.0	50	31	19	39.5	13.0	1.5	0	23.5	0	20.5	2.0	Chest examination negative
12:30 P.M.	8,200	28.0	50	29	21	47.0	11.0	1.5	0	24.5	1.0	14.0	1.0	Chest examination negative
3:30 P.M.	9,900	28.0	50	29	21	32.0	13.5	3.0	0	31.0	0	20.5	0	Slight coughing, few râles in chest*
8.00 P.M.	9,500	29.0	48	23	29	34.5	7.5	2.0	0	27.5	0	26.0	2.5	Slight coughing, few râles in chest*
10/7 9:00 A.M.	9,550	28.0	44	22	34	38.0	10.5	1.5	0	22.0	0	26.0	2.0	Chest examination negative
3:00 P.M.	8,650	24.0	50	32	18	46.0	11.0	1.0	0	22.5	1.0	18.0	0.5	Chest examination negative
11:00 P.M.	7,650	26.0	38	35	27	30.0	8.0	0.5	0	27.5	2.0	31.0	1.0	Chest examination negative
10/8 9:00 A.M.	7,450	27.0	46	28	26	45.5	6.5	0.5	0	26.0	0.5	21.0	0	Chest examination negative
4:00 P.M.	6,950	25.0	49	30	21	33.0	8.5	1.0	0	31.5	0	24.5	1.5	Chest examination negative, discharged
10/10 4:00 P.M.	10,200	14.0	44	45	11	37.5	8.0	1.0	0	18.0	1.5	32.5	1.5	Chest examination negative

*Patient awakened from sleep.

asthma on the seventh day of sulfathiazole therapy (combined nasal installation and oral administration). He remained in severe status asthmaticus for three days, his asthma persisting for seven days. After he had been symptom-free for a week he submitted to the ingestion of 2 Gm. of sulfathiazole at 9:00 A.M., October 5, 1943. He developed a severe attack of asthma as evidenced by his record of symptoms and vital capacity as shown in Table II and Chart 3. From this data it will be noted that he did not develop a striking change in his total leucocyte count as in the preceding case, the most marked variation occurring in the eosinophile determinations. After a temporary elevation one hour following ingestion, the eosinophiles diminished to 4 per cent at four hours, corresponding to the peak of his asthma symptoms. They remained at low levels during the attack, following which they showed a surprising elevation reaching approximately 30 per cent of the differential count at the end of twenty-four hours, then persisted at high levels throughout the period of observation. A slight increase in young myeloid cells also occurred in this case.

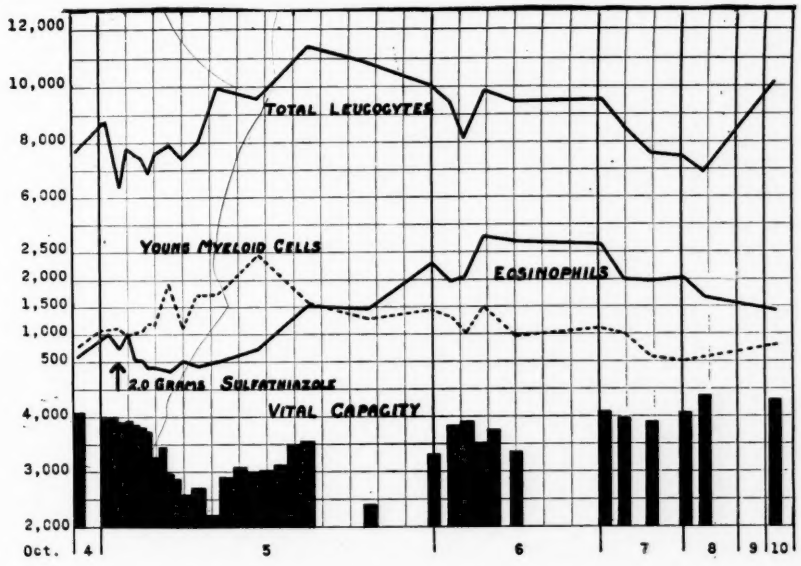

Chart 3.—Case 2. (F. F.) Cellular response and vital capacity determinations following the ingestion of 2 Gm. of sulfathiazole.

CASE 3.—M. M., female, aged 34 years, with a past history of atopic dermatitis, allergic rhinitis, and bronchial asthma, developed manifestations of sensitivity to sulfadiazine during the course of pneumonia in 1942. A year later 0.5 Gm. of sulfadiazine was taken during an upper respiratory infection and was followed by headache, a generalized rash, and an attack of bronchial asthma for the first time in three years.

After the lapse of another year, the same dose was repeated experimentally on Feb. 5, 1944. Although not followed by clinical asthma,

*Patient awakened from sleep.

TABLE III

CASE 3. (M. M.) THE BLOOD RESPONSE AND SYMPTOMS FOLLOWING THE INGESTION OF 0.5 GM. SULFADIAZINE

DATE		TOTAL WHITE COUNT	DIFFERENTIAL COUNTS										SYMPTOMS
			COUNTING CHAMBER				STAINED FILM						
			EOSINOPHILES (9 SQUARES)	POLYMORPHONUCLEARS	MONONUCLEARS	EOSINOPHILES	POLYMORPHONUCLEARS	STABS	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	MONOCYTES	
2/5	9:15 A.M.	12,100	3.6	66	30	4	56.5	4.0	7.0	0.5	30.5	1.5	
	9:25 A.M.	12,250	3.8	65	31	4	54.5	4.5	6.5	0.5	33.0	1.0	
	9:30 A.M.	*0.5Gm. Sulfadiazine administered orally*											
	10:00 A.M.	6,250	4.2	64	33	3	62.0	5.0	7.0	1.5	23.5	1.0	
	10:30 A.M.	6,800	5.8	67	31	2	60.5	8.0	9.5	1.0	20.5	0.5	
	11:00 A.M.	10,200	4.5	67	27	6	63.5	8.5	7.0	0.5	20.0	0.5	
	11:30 A.M.	9,200	4.0	66	28	6	60.5	7.0	6.5	0	25.0	1.0	Flushed face
	12:00 N.	8,800	3.7	64	31	5	63.0	6.5	8.5	0.5	20.0	1.5	Frontal headache, mild; malaise
	3:00 P.M.	12,350	3.2	75	21	4	63.0	8.5	5.0	1.5	20.5	1.5	Frontal headache, severe; malaise
	8:00 P.M.	13,000	3.8	71	24	5	65.0	8.0	10.0	1.5	14.5	1.0	Frontal headache, extreme fatigue
2/6	10:30 A.M.	10,250	7.4	67	23	10	60.0	7.0	5.0	0.5	25.5	2.0	Residual fatigue only
	9:00 P.M.	6,700	7.0	65	29	6	56.0	6.5	6.0	1.0	30.0	0.5	Symptom-free
2/7	9:30 A.M.	7,600	7.3	61	28	11	57.5	8.0	4.0	0.5	29.0	1.0	
2/8	9:30 A.M.	7,450	5.9	70	25	5	58.5	9.0	5.0	1.0	26.0	0.5	
2/9	9:30 A.M.	6,850	5.8	61	31	8	60.0	6.5	6.0	0	25.5	2.0	
2/10	9:30 A.M.	6,100	6.1	63	31	6	62.0	5.0	5.0	0	26.0	2.0	
2/12	9:30 A.M.	8,100	3.0	68	26	6	64.0	4.5	5.0	0.5	25.5	0.5	

she developed a diminution in her vital capacity, severe headache, and general malaise. As may be observed from Table III and Chart 4, the total white count dropped precipitously immediately after the drug and then became elevated coincident with the appearance of young myeloid cells in the peripheral circulation. There also occurred an early diminution of eosinophiles followed by a delayed relative eosinophilia.

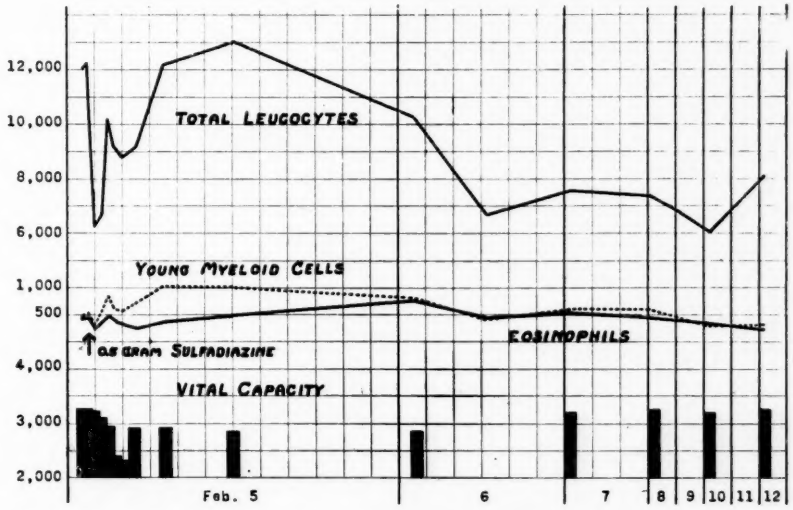

Chart 4.—Case 3. (M. M.) Cellular response and vital capacity determinations following the ingestion of 0.5 Gm. of sulfadiazine.

DISCUSSION

It is evident from widespread usage that, although the majority of individuals tolerate the sulfonamide drugs, others develop unmistakable symptoms of intolerance despite similarities in regard to the clinical indications, dosage, and duration of treatment. It is difficult to interpret the clinical evidence of intolerance occurring during the first course of therapy. It is open to debate whether the underlying mechanism of intolerance developing during the initial course of therapy is due to a chemical poisoning or specific sensitization. However, the immediate and dramatic response which occurs when the drug is again given can be explained only upon the basis of a true allergic reaction. We do not consider the occurrence of crystalluria in this discussion.

The usual delay in the onset of symptoms during the first course of therapy may possibly be attributed to accumulative quantitative chemical effects. However, the fact that these reactions of intolerance most commonly appear during the second week of treatment suggests that some qualitative variation has occurred in the reactivity of the host as the result of a period of exposure. A situation is presented which contains the requirements for the development of an antigen-antibody phenomenon. Benzene ring containing drugs are known to be potentially antigenic, the time relationship from the initial exposure to

the development of symptoms would permit antibody production. Hageman and Blake[6] pointed out the similarities in the circumstances preceding the onset of clinical symptoms of intolerance to sulfonamides and the production of the delayed type of serum sickness. A period of approximately ten days is essential for the development of clinical evidence of sensitivity in both conditions. Furthermore, certain clinical reactions to sulfonamides, such as drug fever, may become evident with resumption of therapy after a lapse of ten days from the time of the initial dose.[7] This observation is compatible with the presented thesis and is not readily explained on the basis of a "toxic" effect of the drug in the sense of a quantitative chemical poisoning.

This analogy to serum sickness may be carried a step further. Once serum sensitivity has been established in the host, a repeated antigenic exposure calls forth an accelerated type of serum sickness. Similarly, in a patient with a past history of clinical intolerance to a specific sulfonamide, a repeated dose may produce a sharp reaction. The severity of this reaction, as in the serum response, appears to depend upon the degree of sensitivity existing at the time and to a less extent upon the size of the dose received, although more violent reactions tend to follow the administration of larger doses.

Case 1 (A. A.) may be taken as an example of the altered reactivity developing from repeated exposures to sulfathiazole. Two courses of therapy were received without evidence of clinical intolerance or variation in the hematological response. The third course was tolerated clinically, but the patient developed a neutropenia on the third day. The fourth and fifth attempts to prescribe the drug were immediately followed by a severe neutropenia and a violent constitutional reaction after single doses.

Several features of this case are unusual and instructive. It is significant that her previously existing bronchial asthma cleared immediately after the ingestion of the trial dose and that she remained asthma-free for a period of one week. The subsidence of previous allergic symptoms during the period of a second and different allergic response is not an uncommon clinical finding. The prompt occurrence of neutropenia in association with severe constitutional symptoms was striking. The development of a leucocytosis following the neutropenia, dependent in its early stages, at least, upon the presence of many young myeloid forms in the circulation is a feature of the drug reaction which has not been emphasized. Although early attention has been called to the leucocytosis occurring during the course of sulfanilamide therapy, this response from a trial dose in a known reacting patient was first carefully studied by Schlesinger and Mitchell.[8] They reported a leucocytosis with an increase in polymorphonuclears within a few hours after the trial administration of a test dose in patients reacting unfavorably to a previous course of sulfanilamide therapy. The leucocytosis was often associated

with the production of a rash and constitutional symptoms. They did not note the presence of an initial neutropenia in counts performed at hourly intervals after ingestion and did not comment on the presence of young myeloid forms in the blood during the induced reaction.

So-called "leucemoid reactions" have been reported in patients receiving sulfonamide therapy, counts reaching as high as 100,000 cells per millimeter of blood. These reactions occurred after continued sulfonamide therapy and were usually associated with hemolytic anemia. In this case the erythrocyte count or hemoglobin determination did not vary from the preingestion normal during or following the reaction. There was no clinical evidence of a hemolytic phenomenon although fragility and other special studies were not done.

The cellular response in this patient was not limited to the myeloid cells as evidenced by the absolute diminution in the number of eosinophiles and lymphocytes. There was a definite correlation between the period of eosinopenia and the constitutional symptoms as measured by elevations in the temperature and pulse. It is well known that eosinophiles tend to diminish in the peripheral circulation during the height of acute allergic symptoms and reappear with the subsidence of symptoms. The lymphopenia, reaching a low point six hours after ingestion and persisting at low levels for several hours is a further striking reaction which, as far as we know, has not been described as part of the drug allergic response. The question might be raised as to whether the lymphocytes are reduced relatively as a result of the marked myeloid reaction. The degree of lymphopenia in this case suggests some additional mechanism.

This case also illustrates the point that the total white cell count performed with the standard acetic acid diluent in the absence of a differential count might fail to detect a major blood response to a sensitizing drug. For instance, six hours after the ingestion of sulfathiazole the total leucocyte count was normal (7,850), although the film differential count reveals that 66 per cent of the cells were young myeloid forms and that there was an absolute diminution from previous levels of both the lymphocytes and eosinophiles. However, this abnormality was readily detected by performing the total leucocyte count with the propylene glycol aqueous diluent. The superiority of the latter diluting fluid in comparison with the standard acetic diluent has been reported elsewhere.[1]

Furthermore, assuming that a differential count had been performed at six hours with either the counting chamber or film technique, and that the sulfonamide drug had been prescribed in the presence of a severe infection, the shift to the left as well as the other blood changes could readily have been ascribed to the presence of the infection rather than as a result of the drug administration. It becomes apparent that the early cellular changes resulting from sulfonamide therapy, especially after repeated doses, must be carefully differentiated from those result-

ing from an infection. A single blood count during the course of a drug reaction may be misinterpreted; the true picture may not become evident unless repeated blood determinations are made.

The nearly identical contours of the differential counts as determined from the stained film and the counting chamber techniques attests to the reliability of the propylene glycol method. This agreement is noteworthy in that the variations within the differential count were correctly appraised from the counting chamber determinations performed immediately and completed prior to obtaining the results of the film differential count.

In Case 2, the patient (F. F.) failed to show the sharp neutropenia after trial ingestion of sulfathiazole as in the first case. Nevertheless, the total leucocyte count dropped slightly and there was a diminution in the eosinophiles. The delayed postreactive eosinophilia remained the most significant cellular reaction in this case; this high value, approximately 30 per cent, might possibly be explained on the fact that the patient had a moderate eosinophilia prior to ingestion. As far as we are aware, changes of this magnitude in the number of eosinophiles during the course of and following a sulfonamide reaction have not previously been reported.

A reaction of the same general pattern was observed in the third patient (M. M.) although the cellular changes were evident to a less striking degree than in the preceding cases. Perhaps a less marked degree of sensitivity existed at the time of the test dose; also a smaller trial dose was administered. There is the additional fact that sulfadiazine may be a less potent sensitizing agent than sulfathiazole, clinical observations tend to support this view.

It is of more than passing interest that of these three cases of bronchial asthma, the trial dose of a sulfonamide drug resulted in the prompt, temporary improvement of the bronchial asthma in one instance, the production of a severe asthmatic paroxysm in another, and a slightly diminished vital capacity suggestive of a minimal bronchial spasm in the third.

SUMMARY

1. The trial ingestion of a specific sulfonamide drug in three asthmatics known to be clinically drug sensitive resulted in an initial diminution in total leucocytes and eosinophiles; this was followed by an increase in leucocytes due, in part, to the presence of young myeloid cells.

2. After the constitutional symptoms had subsided, the eosinophiles either returned to the preingestion count or showed a definite increase above that level.

3. The clinical and hematological response in these cases supports the thesis that an allergic mechanism is responsible for the described reactions.

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STUDY OF ASTHMATICS RETURNED FROM OVERSEAS

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THE initial 200 cases of asthma returned from oversea theaters, consecutively admitted to the allergy service of a large Army hospital, comprise the material for this study. These patients were returned from their oversea locations because of asthma of such severity as to incapacitate them for further duty. Symptoms continued while under treatment in evacuating hospitals, during the boat trip back, and after return to the United States. Opinions arrived at are based solely upon the group of returned asthmatics studied at this hospital. No conclusions may be drawn from these data with regard to the percentage of troops developing asthma in various geographic locations, or to the total number of men evacuated from these areas because of asthma.

The great majority of patients manifested their asthma while in the tropics. The following territories lie between the Tropic of Cancer and the Tropic of Capricorn: the Belgian Congo, Solomon Islands, British Samoa, New Hebrides, Fiji Islands, New Guinea, northern Australia, New Caledonia, Panama Canal Zone, southern India, and the Hawaiian Islands. These regions have two factors common to the tropical zone: high temperature and excessive humidity. Within these areas there originated 183 cases representing 91.5 per cent of the total. The remaining 17 cases, 8.5 per cent, were returned from North Africa (20° to 40° north latitude), England (50° to 60° north latitude), Aleutians (50° to 60° north latitude), Iceland (60° to 70° north latitude), and southern Italy (38° to 42° north latitude).

One hundred thirty-seven patients (68.5 per cent) gave a history of bronchial asthma prior to entry into the Army. These included seasonal pollen asthma and perennial asthma. In some, the asthma had ceased in civilian life; in others the history of symptoms was present at the time of induction. In many, there was a history of asthma of more than ten years' duration with continuation of symptoms in Army camps in this country. The onset of asthma, in such cases, obviously was not in foreign countries. However, this group evidenced marked increase in the frequency and severity of their episodes while on foreign duty. Each of these soldiers was in an Army camp somewhere in the United States for a period of months or years prior to overseas service. The severity of his asthma did not necessitate prolonged hospitalization or presumably render him unfit for military duty while in the United States. These are facts in evidence of the increase in degree of the asthma as manifested by repeated or constant dyspnea which rendered the soldier unfit for duty.

TABLE I

GEOGRAPHICAL SOURCE OF PATIENTS

LOCATION	NUMBER OF CASES	PERCENTAGE OF CASES
Tropical—91.5 per cent		
Solomons	70	35
New Hebrides	18	9
Fiji Islands	9	4.5
New Guinea	8	4
Australia	11	5.5
New Caledonia	25	12.5
Hawaii	28	14
Canal Zone	8	4
India	4	2
Belgian Congo	1	0.5
British Samoa	1	0.5
Nontropical—8.5 per cent		
North Africa	10	5
Italy	1	0.5
England	3	1.5
Aleutians and Iceland	3	1.5
Total	200	100.0

TABLE II

NUMBER OF NEW AND PRE-EXISTING CASES FROM EACH AREA

LOCATION	TOTAL NUMBER OF CASES	NEW CASES (%)	PREVIOUS ASTHMA (%)
Solomons	70	21.4	78.6
New Hebrides	18	66.6	33.4
Fiji Islands	9	55.5	44.5
New Guinea	8	25	75
Australia	11	27.2	72.8
New Caledonia	25	36	64
Hawaii	28	25	75
Canal Zone	8	37.5	62.5
India	4	0	100
Belgian Congo	1	0	100
British Samoa	1	0	100
North Africa	10	50	50
Italy	1	0	100
England	3	0	100
Aleutians and Iceland	3	66.6	33.4

Sixty-three (31.5 per cent) were new cases who developed their initial attack of dyspnea, wheezing, and tightness of the chest with physical signs of bronchial asthma while on duty in the various regions listed.

Table II presents the proportion of new cases to cases of preexisting asthma with exacerbation in each area.

Table III presents the percentage of the 63 new cases of asthma developing in the respective locations. It is noteworthy that 56 cases, 88.9 per cent of the new cases, developed asthma in tropical areas with humid, hot climates.

The group was composed of young adult males, white and Negro. The youngest patient was 19, and the oldest 45 years. There were 138 pa-

TABLE III

SOURCE OF NEW CASES OF ASTHMA

LOCATION	NUMBER OF NEW CASES	PERCENTAGE
Tropical—88.9 per cent		
Solomons	15	23.8
New Hebrides	12	19.0
Fiji Islands	5	7.9
New Guinea	2	3.2
Australia	3	4.8
New Caledonia	9	14.3
Hawaii	7	11.1
Canal Zone	3	4.8
India	0	0
Belgian Congo	0	0
British Samoa	0	0
Nontropical—11.1 per cent		
North Africa	5	7.9
Italy	0	0
England	0	0
Aleutians and Iceland	2	3.2
Total	63	100.0

tients (69 per cent) in the decade of 19 to 28 years inclusive, 54 cases (27 per cent) in the decade of 29 to 38 years inclusive, and only 8 cases (4 per cent) 39 years or older.

METHOD OF STUDY

The study of each case included the following procedures: (1) A complete history with emphasis on a detailed allergic history. Especial inquiry was made for any manifestation of allergy in the past history, a description of the environment and circumstances in which the asthma first appeared or became more pronounced while in the Army, when the attacks occurred, and what factors served as aggravants. The complete progress of the asthma while overseas, in hospitals, during the ocean voyage to the United States, and since the return to this country was noted. (2) Complete physical examinations were performed. (3) Laboratory studies included a blood count, serologic examination, urinalysis, sputum examination for tubercle bacilli and eosinophiles (sputum culture and search for fungi in certain cases), stool cultures, and stool examinations for ova and parasites. Any other laboratory studies that might be indicated by other coexisting diseases were performed. Nasal smears for eosinophiles were examined in allergic rhinitis. (4) X-ray studies of the nasal sinuses and chest were performed on all patients. (5) Consultations: (a) Dental examination and treatment for any foci of infection; (b) nose and throat examinations including transillumination of the sinuses; (c) other consultations as indicated by the existence of other complaints. (6) Allergy tests. The intradermal method of testing was employed. The extracts of inhalants used for testing were prepared and standardized in the laboratories of the Fourth Service Command. The following inhalants

were routinely tested: house dust, cat dander, dog dander, horse dander, rabbit dander, sheep dander, duck feathers, goose feathers, chicken feathers, orris, cottonseed, kapok, ragweed and timothy pollens (in strengths including 10,000 pollen nitrogen units per cubic centimeter), and molds including alternaria, aspergillus, hormodendrum, penicillium, corn smut, monilia, cephalothecium. (Mold dilutions were 1:10.) Food tests were done, where indicated, with extracts prepared in the allergy clinic of the Jefferson Medical College Hospital. Both stock and autogenous catarrhal vaccines were used for skin testing. (7) Bronchoscopic examination and bronchograms were performed by the chest service in cases with evidence of lung pathology complicating bronchial asthma. The aspirated bronchial secretions were cultured routinely.

ONSET

In the analysis of the history of the onset in the new cases and the recurrence of symptoms in former cases, it became apparent that the asthma was conditioned by three factors, namely climate, dust, and infection. By climate is meant either high humidity (relative and absolute) with increased temperatures and daily rains over prolonged periods of time as prevail in the tropics, or the weather was cold and damp with frequent rain common to England, Africa, Italy, and the Aleutians.

Horack[1] stated that the average rainfall in the Solomon Islands is 130 to 150 inches per year. "The hot (76.5° to 92.5° F.) and humid (81° relative humidity) atmosphere is not a healthy one. The average rainfall in New Guinea is 100 to 130 inches per year."[2] The same climatic factors are present in the other areas listed in the tropics. There are seasons when there is rain every night with clear, dry weather during the day, though at times it rains frequently during the day also. Each area has a dry period of the year when there is but little or no rainfall. A case of asthma with onset due to climatic factors would be exemplified in a patient, aged 21 years, who gave a history of perennial bronchial asthma in childhood. He has been free from symptoms of asthma for five years prior to entering the Army and had had no asthma while in the Army in the United States. He was well on arrival in the Belgian Congo. He had no asthma until a rainy season began which lasted three weeks. Then he developed continuous bronchial asthma which cleared only when the rains ended, and he did not have a single attack of asthma in the two months of dry weather which followed. A second period of heavy rains occurred, during which time the patient had constant asthma until he was moved to another area which was dry. He remained symptom-free there, on the boat trip en route to the United States, and during a three-month period of observation in this country. He was then returned to duty in a temperate climate. Here, then, is a known asthmatic, free from symptoms for years, who had severe asthma on two occasions, only during a period of constant rain.

He was well in the location in which he was stationed during hot, dry weather and also after leaving the area. Any air-borne etiological agent such as pollen, mold, or dust would be more prevalent during dry weather and be washed out of the air during weeks of heavy rain.

Another example of climatic factors causing the onset of asthma is the history of a patient who had had asthma for seven years, from 13 to 20 years of age. All symptoms ceased in 1939, and he remained well while in Army camps in the United States. He arrived in the New Hebrides in August, 1942, and was well until September, 1942, when the rains began, and his symptoms recurred. It rained every night and morning, and his asthma occurred every night and cleared during the daytime when it was hot, dry, and the sun was shining.

Another man, aged 32 years, with a negative past history of allergy arrived in the South Pacific in May, 1943. Onset of dyspnea and wheezing first occurred in September, 1943. While on outpost duty in the Solomons it rained every night, and he slept in a wet foxhole for fifteen nights. The foxhole was filled with water, and he was literally "soaked to the skin." It was under these conditions that dyspnea and wheezing first occurred, and then symptoms recurred only at night during the rain. The asthma became constant and continued during the boat trip across the Pacific and was still present in this hospital when he was discharged in January, 1944.

Exposure to dust was a second cause of the onset of asthma. This type is illustrated by a patient, aged 30 years, who had a negative past history of allergy. He arrived in New Guinea in September, 1942, and was well during the rainy season. He was a truck driver, and in dry weather in July, 1943, while doing an increased amount of driving on dusty roads with consequent heavy exposure to dust, he developed asthma. He was worse in dry weather, and noticed that he would be much worse when driving behind other trucks when the exposure to dust was increased. Asthmatic attacks ceased on his return to the United States. Dust exposure caused the onset in 32 cases (16 per cent).

The third type of onset, that following infection, is illustrated in the case of a patient, aged 44 years. Onset of asthma followed an attack of bronchopneumonia in 1942 with an increase of severity of the asthma after a second attack of pneumonia in 1943. Other cases had their onset after "colds" in damp or cold weather. Nine patients (4.5 per cent) thus had their onset after infections.

A study of the onset of the 200 cases reveals that the onset was due to (1) climatic factors in 159 cases (79.5 per cent), (2) dust exposure in 32 cases (16 per cent), and (3) infection in 9 cases (4.5 per cent).

PRECIPITATING FACTORS

After the initial onset, further attacks were precipitated in the various cases by a single factor of onset, as climate, or in most cases by a com-

TABLE IV

PRECIPITATING FACTORS OF SUBSEQUENT ATTACKS IN 200 CASES

FACTOR	NUMBER	PERCENTAGE
Climate, alone	24	12
Dust, alone	14	7
Infection, alone	0	0
Dust and climate	114	57
Dust and infection	10	5
Climate and infection	8	4
Climate, dust, and infection	30	15
Total	200	100

bination of the three factors of climate, dust, and infection. The precipitating factors of further attacks of asthma in the 200 cases are listed in Table IV.

Table IV reveals that climatic factors alone or combined with other factors played a role as a precipitating factor in 88 per cent of the cases. Dust, alone, or combined with other factors, was a precipitating factor in 84 per cent of the cases. Infections of the respiratory tract played a role in 24 per cent of the cases. Eighty-one per cent had their asthmatic attacks precipitated by more than one factor.

CASE REPORTS

An example of dust and climatic factors precipitating asthmatic attacks is the following case. A patient, aged 21 years, formerly a farmer, had had attacks of asthma since childhood when exposed to dust, as in a barn. He arrived in England in September, 1943. The weather was damp, and rains fell frequently. Asthma became severe and constant three weeks after arrival while doing outdoor guard duty in the rain. His symptoms were milder in dry hospital buildings in England, and his asthma was mild after his return to the United States. Skin tests were positive to dust and feathers. To rule out other pulmonary pathology, bronchoscopic examination was performed; the bronchial mucosa was atrophic. Culture of sputum obtained by bronchoscopic aspiration was sterile. Bronchograms were negative. The nasal sinuses were clear. There was no evidence of infection in this case of perennial bronchial asthma caused by allergic sensitivity to dust with marked increase in the severity of symptoms when exposed to a damp, cold climate.

An example of climate and infection operating jointly is illustrated by a private, aged 23 years, who had a negative history of any allergic condition prior to Army service. He had no symptoms after entering the Army while in this country. In March 1943, he arrived in the New Hebrides where he slept on the ground in the rain. Two days after his arrival he "caught cold" and developed dyspnea, wheezing, coughing, and expectoration. Symptoms were still present in December, 1943, when he was admitted to a hospital. The diagnosis was (1) chronic bronchitis, and (2) perennial bronchial asthma. The symptoms had

been more severe during the rainy season in the New Hebrides and following upper respiratory infections. Sputum culture contained *Streptococcus viridans.* Skin tests were positive to dust and catarrhal vaccine. Treatment with injections of dust extract, catarrhal vaccine, and a course of sulfadiazine failed to clear the condition. While in this hospital symptoms were more severe on rainy days and following respiratory infections.

An example of dust, climate, and infection operating as precipitating factors in the same case is illustrated by a patient, aged 23 years, who had chronic, perennial, bronchial asthma since childhood. Positive skin tests to dust, feathers, and ragweed and timothy pollens were obtained. Exposure to dust and resulting asthma forced him to give up his occupation as a farmer. Pneumonia occurred in 1932, 1935, and 1937. Following the last attack of pneumonia the asthma became constant. He arrived in New Caledonia in September, 1943, and asthma immediately became more severe in the damp climate and continued in hot and rainy weather in New Georgia. He was evacuated in December, 1943, because of severe asthma which was present on admission to this hospital. His asthma was constant. While under observation he had flare-ups on days of rain, after respiratory infections, and after exposure to dust while dusting closet shelves.

The physical signs were those typical of bronchial asthma, alone, in 175 cases (87.5 per cent); of bronchitis combined with bronchial asthma in 16 cases (8 per cent); of emphysema with bronchial asthma in 6 cases (3 per cent); and physical signs were negative in 9 cases (4.5 per cent). (The asthma had cleared in these 9 cases prior to admission to this hospital.)

The following associated manifestations of allergy were present in 200 cases: (1) perennial allergic rhinitis, 78 cases (39 per cent); (2) hay fever, 14 cases (7 per cent); (3) urticaria, 1 case (0.5 per cent); and (4) eczema, 1 case (0.5 per cent).

It is noteworthy that the incidence of hay fever, 7 per cent, was low for a group of unselected cases of asthma. This is evidence against the etiological importance of pollen sensitivity in these cases. The hay fever existed prior to induction in the Army in several of the 14 cases.

Sputum examinations were positive for acid-fast bacilli in only one case. This was a patient, aged 21 years, who was born and lived in Puerto Rico. He presented a negative past history of allergy and was well during the first two years of Army service. His onset of bronchial asthma occurred one month after he reached Panama Canal Zone during the rainy season. Throughout the period of daily rains the patient developed dyspnea, wheezing, tightness of the chest, and coughing. Symptoms continued after arrival at this hospital. Intradermal tests to dust and feathers were positive. Bronchoscopic examination revealed acutely inflamed left bronchial mucosa with thin mucoid secretion. Aspirated secretions were negative for tubercle bacilli. Only one posi-

tive sputum was found, and the chest service found no evidence of pulmonary tuberculosis. The asthma continued to recur, particularly on damp days despite desensitization with dust extract, mixed catarrhal vaccine, and the usual measures for symptomatic relief.

The sputum examinations were negative for eosinophiles in a majority of the patients. The predominate organisms in the positive sputum cultures were beta hemolytic streptococci, *Streptococcus viridans,* and *Staphylococcus aureus.*

COEXISTING DISEASES

Coexisting diseases found in this group included five cases of dysentery caused by *Endamoeba histolytica.* There were also eleven miscellaneous conditions, including hypertension, gastric ulcer, arthritis, underweight, and syphilis.

In the five cases of dysentery due to amoebiasis there was no evidence that the amoebiasis was an antigenic factor in the asthma as there was no relationship between the onset of dysentery and asthma, and treatment with the elimination of the amoebiasis did not influence the asthma.

The importance of the role of psychogenic factors in the etiology of asthma was considered. Many of these patients were in actual combat, underwent air bombardment, slept in wet clothes in wet foxholes, and faced the hardships of life in the jungles. Bearing in mind the many causes of anxiety that existed, it was important that the role of psychogenic factors be evaluated. Any patient presenting symptoms such as nervousness, tremors, insomnia, depression, and anxiety was referred to the neuropsychiatric service for study. In no instance were such factors found to be of etiological significance in the production of asthma.

SKIN TESTS

Routine skin tests with inhalant extracts, by use of the intradermal technique, gave positive reactions as listed in Table V. The reactions were read as slight, moderate, or marked. A slight reaction consisted of a wheal at least 0.5 cm. in diameter with an associated erythematous flare following a test dose of 0.01 c.c. of extract.

It is apparent that the great majority of the cases were skin reactive. Ninety-eight per cent were skin-sensitive to dust; 85.5 per cent were skin-sensitive to feathers. Only a minority were skin-sensitive to pollens —grass pollen (30.5 per cent) and ragweed pollen (33 per cent).

A number of the twenty-eight cases from Hawaii and of the eight cases from the Canal Zone had skin tests performed at General Hospitals in those areas. Tests there for local pollens such as those of sugar cane, cocoanut, monkey pod, and various local grasses were negative in most of these cases.

Tests were done with an autogenous dust extract labeled "South Pacific Dust" in a group of patients from the South Pacific.

TABLE V

POSITIVE SKIN REACTIONS IN 200 CASES

ANTIGEN TESTED	NUMBER OF CASES WITH POSITIVE REACTIONS	PERCENTAGE OF CASES
Dust (saturated solution)	196	98
Feathers (0.1 mg. N/c.c.) (duck, goose, and chicken)	171	85.5
Timothy pollen (10,000 PNU/c.c.)	61	30.5
Ragweed (combined) (10,000 PNU/c.c.)	66	33
Danders (cat, dog, horse, etc. 0.01 mg. N/c.c.)	42	21
Catarrhal vaccine	33	16.5
Molds	9	4.5
Orris	6	3
Cottonseed	1	0.5
Kapok	11	5.5

The development of asthma caused by allergy to new foods is improbable in this group. The diet of these 200 patients is rigidly controlled as compared to the diet of any similar group of civilians traveling abroad. The men were fed the same Army mess overseas as in the United States. The men in New Guinea, the Solomons, New Hebrides, Fiji Islands, and other South Pacific locations ate "C" rations. That is, their diet consisted of processed canned foods from the United States. Practically no local new foods were available in many locations.

More mutton was eaten in Australia than Americans eat at home. Certain local fruits, such as mangoes, were eaten in some areas, but the asthma persisted in these cases after the patients' return to this country when the few unusual foods were not available.

Feather pillows were not available in most areas, and the men were not exposed to feathers.

Nose and throat examination revealed various abnormalities of the nasopharynx. There were 78 cases of perennial allergic rhinitis. A number of patients had deviated nasal septa, diseased tonsils, and acute catarrhal rhinitis. X-rays of the nasal sinuses were positive for thickened membranes and clouding of the sinuses in various instances, and a few intrasinus polyps were present. There was only one case, however, in which the asthma cleared after drainage of a purulent infection of one antrum. In this patient the asthma had its initial onset in the South Pacific and subsided promptly after drainage of the maxillary sinus. In the remaining 199 cases suppurative infection of the sinuses was not demonstrated.

Bronchoscopic examinations were done by the chest service on 25 cases. Two patients were found to have a markedly inflamed bronchial mucosa with much thick secretion. Cultures of these secretions in two cases were positive for beta hemolytic streptococci. The remainder of the cases other than the one with positive sputum for tubercle bacilli

were negative on bronchoscopic examination or were reported to have a pale or atrophic mucosa. Bronchograms, with the installation of lipiodol, were done on all 25 cases. Only one had evidence of bronchiectatic changes. This was one of the two patients with inflamed bronchial mucosa and purulent bronchial secretions.

TREATMENT

Treatment included all recognized allergic procedures. Patients were hospitalized in the comparatively dust-free atmosphere of clean, bare hospital wards, and all feather pillows were replaced with hair pillows.

Conventional medication such as potassium iodide, ammonium chloride, ephedrine sulfate alone or with aminophylline orally, epinephrine by injection, theophylline or aminophylline given intravenously or the latter by rectal installation, helium and oxygen inhalations, and ether in oil, administered intramuscularly, gave more or less indifferent relief.

Epinephrine hydrochloride, 1:100 subcutaneously, and epinephrine in oil, 1:500 intramuscularly, were used repeatedly for symptomatic relief. In severe attacks of asthma, epinephrine in oil gave only temporary and partial relief for periods of from two to six hours.

Desensitization with injections of dust extract, alone, was carried out in 27 cases. Dust extract combined with a mixed catarrhal vaccine (both stock and autogenous vaccines were used) were given to 172 patients. Mixed catarrhal vaccine alone was given in one case. Coseasonal ragweed pollen therapy was administered to two patients.

In cases of chronic perennial bronchial asthma with associated bronchitis, postural drainage combined with hyperventilation, produced by the inhalation of carbon dioxide and oxygen was used. This method was employed in accordance with Bonyai and Cadden's[4] suggestion that carbon dioxide by inhalation has an expectorant effect, and that hyperventilation with respiratory excursions of greater depth produces bronchial dilatation. This procedure in our cases failed to increase the amount of sputum raised, and often increased the degree of dyspnea and the feeling of tightness in the chest.

A course of sulfadiazine orally was administered to sixteen patients with streptococci or staphylococci in their sputum cultures. The dosage was 4 Gm. daily for seven to ten days. In three cases the sputum became thinner and less copious while the drug was administered. There was no relief of asthma with the use of sulfadiazine.

The use of penicillin in cases of chronic bronchitis and chronic bronchial asthma has been contemplated but not instituted as yet. Bronchoscopic drainage in the cases bronchoscoped afforded no permanent relief.

RESULTS

The results of treatment of these 200 cases of chronic perennial bronchial asthma are divided into three groups: (1) The cases which cleared

completely and remained free from asthma were considered well and were returned to duty. There were 24 cases (12 per cent). (2) Cases which improved with treatment. The attacks of asthma were less frequent, shorter in duration, and of less severity. These cases were improved but continued to have attacks and could not be returned to duty. There were 125 cases (62.5 per cent) in this group. (3) Cases which remained unchanged and had constant symptoms and signs of asthma, 51 cases (25.5 per cent).

Treatment afforded relief to 74.5 per cent (partial relief, 62.5 per cent; complete, 12 per cent) of this group of 200 cases of chronic, perennial, bronchial asthma. On the other hand, treatment over a period of several months failed to clear completely 62.5 per cent and afforded no improvement to 25.5 per cent. A total of 88 per cent of the 200 cases continued to have recurrent or continuous attacks of asthma, but it will be recalled that 68.5 per cent of the cases had asthma for years prior to entering the service.

Chronic perennial bronchial asthma of the type existing in these cases was not completely relieved by the therapeutic measures available in 88 per cent of the cases.

It is noteworthy that these patients, as a group, continued to have attacks of asthma of increased severity on damp days while in this hospital. This particular hospital is situated in the Mississippi Valley. The average annual rainfall locally is 52 inches over a fifty-year period, affording one of the dampest areas in the country. A portion of these patients would probably fare better in an area of low humidity.

DISCUSSION

When the first group of about 50 cases arrived from various areas in the South Pacific the problem of the etiological factor causing asthma in those areas arose. O. C. Durham, Chief Botanist, Abbott Laboratories, was consulted for the data on air-borne allergens in the South Pacific. He stated, "Tropical areas do not have the flora or the climate conducive to the development or spread of air-borne pollens and fungus spores."[5]

Concerning pollen studies in Australia and New Zealand Durham stated, "The air-borne pollens of southern Australia have been studied extensively. Grass pollens are more important clinically than those of any other type, including trees and weeds. English plaintain pollen is second in importance. . . . Significant amounts of grass pollen are found in the air from mid-August to April. Most of the hay fever occurs in late spring and early summer—October, November, and December. . . . Australia has no ragweed and only one composite, capeweed *(Cryptostemma calendulacea)*. Tree pollens are . . . regarded as potential (usually local) offenders. No work has been done on fungus spore allergy in Australia."[6]

New Zealand: "Grasses are the chief source of hay fever pollens. The grass list includes only cultivated species, such as sweet vernal grass, cocksfoot (orchard grass), the rye grasses, Yorkshire fog (velvet grass), timothy, and bluegrass. The season of pollination extends from October to March with the apex of distribution in December, January, and February."[7]

It should be noted that these studies do not apply to northern Australia, New Guinea, the Solomons, and other areas in the tropics, and tropical areas do not have the flora or the climate conducive to the development or spread of air-borne pollens and fungus spores.[5]

One case nicely illustrates the effect of exposure to grass pollen in southern Australia with the development of hay fever, and the absence of hay fever symptoms in tropical areas. A patient, aged 27 years, had a thirteen-year history of spring and fall hay fever in Boston with a known sensitivity to pollens. Intradermal skin tests were positive to timothy grass and ragweed pollens. There had been no attacks of asthma. He arrived in southern Australia during the grass season and had full-blown symptoms of hay fever during a stay of one week. He then was stationed in New Caledonia, Guadalcanal, and the Fiji Islands. There was no recurrence of any hay fever symptoms after leaving Australia. There had been no asthma in Australia or New Caledonia. He first developed attacks of asthma in Gaudalcanal during rainy weather in January, 1943. Chronic perennial bronchial asthma continued in the damp climate in the Fiji Islands, on the ship en route here, and was present on admission to this hospital in December, 1943. The pollens in Australia that caused hay fever did not cause asthma. The factors in Guadalcanal and the Fiji Islands that caused asthma did not cause hay fever.

Patients returning from the South Pacific had barracks bags containing articles of clothing, blankets, and other equipment. These bags had been packed in the South Pacific and had not been opened since leaving there. They unpacked the bags in a closed room, and each man promptly had an attack of asthma. The bags and their contents were dusty and the attacks may have been due to dust. In an attempt to exclude other factors, such as pollens, the bags and their contents were vacuum cleaned. Slides were made by mounting dust obtained in a glycerine jelly containing a methyl green stain. Numerous slides were examined, and I found a total of only three grass pollen grains and one unknown pollen grain. Cultures of the dust were made at the laboratories of the Fourth Service Command and failed to grow any molds.

In addition there were only fourteen cases (7 per cent) in the entire group who had clinical hay fever, and this figure includes those who had hay fever in this country prior to going overseas. Sixty-nine and five-tenths per cent of the patients had negative skin tests to timothy grass pollen, 10,000 pollen nitrogen units per cubic centimeter. Sixty-

seven per cent had negative skin reactions to ragweed pollen, 10,000 units, and 95.5 per cent of the patients had negative skin tests to mold extracts, 1:10 dilution.

In an effort to determine the presence of any unidentified antigen in the dust obtained from the barracks bags returned from the South Pacific, an extract of the dust was made. This dust was labeled "South Pacific Dust." Skin tests were performed intradermally, simultaneously, with our usual house dust extract and "South Pacific Dust." The reactions to "South Pacific Dust" were equal to, or smaller than, the reactions to regular dust in the same patients. There were no instances in which the "South Pacific Dust" gave a larger reaction than ordinary house dust. This would indicate that there was no antigenic factor in the dust from South Pacific areas capable of eliciting any greater skin reactivity than the constituents of ordinary house dust extract.

The above facts are evidence against the possibility that the perennial asthma that developed in tropical regions was caused by exposure and resultant sensitivity to any unknown air-borne pollens or molds. In addition it should be remembered that most of the patients had their asthma during heavy rainfalls. Moreover, these patients had long voyages across oceans when they were far away from pollens. They continued to have asthma during the boat trips.

High temperatures and high humidity have an effect on the respiration of normal individuals. Rosenau[9] states that persons remaining at rest in saturated air at 95° F. for one hour will have an increase in depth and rate of respiration with puffing on slight movement. Also heat causes respiration to become more rapid but at the same time shallow.[10] Heat is more trying when air is humid. As a result in tropical climates there is a loss of carbon dioxide which leads to alkalosis.

The adverse effect on existing asthma of extremes of temperature and excessive humidity is well known. Tuft[11] states that attacks occur more often where there are variable temperatures and degrees of humidity. The asthmatic is more comfortable in areas of low humidity. The patients in this group were in areas in which the common factor was high humidity.

SUMMARY

1. Two hundred patients with chronic perennial bronchial asthma were returned from overseas locations, of whom 95.5 per cent continued to have recurrent or continuous asthma after return to the United States. Of the total group, 31.5 per cent had the initial onset of asthma overseas, and 68.5 per cent had a recurrence or aggravation of pre-existing asthma in overseas locations.

2. Of the new cases, 88.9 per cent developed asthma in areas with a hot, humid climate. Of the entire group, 91.5 per cent were returned from tropical areas.

3. The onset of asthma in the new cases and recurrence in previous asthmatics were due to climatic factors in 159 cases (79.5 per cent).

4. In this group of patients, skin reactive to extrinsic allergens, the climate of high humidity with frequent rains was a significant factor in the onset and continuation of chronic, perennial, bronchial asthma

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EVALUATION OF THE HISTAMINE INTRADERMAL TEST AS A GENERAL INDICATOR OF ALLERGY*

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IN A paper on the etiology and treatment of Ménière's syndrome, Atkinson[1] suggested the use of histamine intradermally as a general indicator of the presence of an allergic disturbance. He bases this suggestion on the fact that "there is considerable evidence to show that the manifestations of allergy are possibly due to the release of histamine or of a histamine-like substance into the affected tissues." With the help of the histamine intradermal test he feels that it is possible to "satisfactorily separate the (histamine) sensitive from the insensitive," the inference being that by this method one can establish whether an individual is allergic or not. On the basis of this reasoning allergy would consist of increased histamine sensitivity. We believe this assumption to be incorrect. Although we strongly subscribe to the assumption that the manifestations of allergy are due to the release of histamine, we do not believe that allergy is enhanced histamine sensitivity, i.e., that allergic individuals are simply more sensitive to histamine than are normal individuals. We, therefore, also feel that it is not possible to determine whether or not an individual is suffering from an allergy on the basis of whether he shows a stronger or less strong skin reaction to histamine.

In the course of earlier work, we had examined the histamine sensitivity of normal and allergic individuals by puncturing histamine into the skin. We did not find any difference in the skin reactivity of the two groups; i.e., the allergic individuals did not react more strongly to histamine than did the normal individuals. In the present investigation we repeated these tests intradermally. We used 0.01 mg. of histamine phosphate as suggested by Atkinson. This amount of histamine was contained in 0.05 c.c. of physiologic saline. The control consisted of 0.05 c.c. of physiologic saline.

All tested individuals reacted to the histamine with a distinct wheal which in no instance measured less than 10 to 13 millimeters. However, this is not a positive reaction according to Atkinson's terminology. His criteria for a positive reaction are "a wide area of erythema 1½ to 2 inches (3.8 to 5 cm.), a large wheal ½ to ¾ inch (1.3 to 1.9 cm.) and the presence of long trailing pseudopodia an inch or more in length which appear in three to five minutes, begin to fade only after twenty minutes, and are still apparent at the end of thirty minutes. Small buds at the edge of the main wheal which fade in ten to twenty minutes are not assessed as positive." According to these criteria none of the

*From the Allergy Clinic, Lenox Hill Hospital, New York, N. Y.

TABLE I

SIZES OF HISTAMINE WHEALS

PATIENT		AGE (YR.)	REACTION			
			HISTAMINE			ALLERGEN EXTRACT
			WHEAL (MM.)	FLARE (MM.)	PSEUDOPOD (MM.)	
A. Nonallergic individuals						
1. M. M.	♀	30	13 by 21	60 by 60	Buds	Negative
2. D. D.	♂	51	14 by 16	50 by 55	None	Negative
3. H. S.	♂	51	13 by 13	25 by 35	None	Negative
4. G. P.	♂	53	15 by 17	30 by 40	12	Negative
5. M. S.	♀	28	10 by 13	35 by 35	Buds	Negative
6. A. M.	♀	49	15 by 17	50 by 55	None	Negative
7. S. K.	♀	27	14 by 14	50 by 55	None	Negative
8. H. B.	♂	38	13 by 14	45 by 45	None	Negative
9. A. G.	♀	26	15 by 15	45 by 50	7	Negative
B. Allergic individuals						
1. Hay fever						
1. J. I.	♂	27	14 by 14	55 by 65	None	Grasses ++++
2. H. L.	♂	45	11 by 14	45 by 55	Small buds	Ragweed ++++ Grasses +++ House Dust +
3. K. D.	♀	47	13 by 15	50 by 60	None	Ragweed ++++ Timothy +++
4. E. B.	♀	25	15 by 15	55 by 60	Small buds	Ragweed + Ash +
5. J. P.	♀	13	12 by 14	45 by 50	None	Ragweed ++++ Plantain ++
6. J. S.	♀	38	12 by 15	40 by 45	Small buds	Ragweed ++++ House Dust ++
7. E. J.	♀	44	12 by 14	35 by 40	Small bud	Ragweed +++ House Dust ++
8. E. L.	♂	60	14 by 17	45 by 50	Small bud	Ragweed +++
9. M. L.	♀	41	14 by 15	50 by 55	Small bud	Ragweed ++ Grasses ++
10. B. Z.	♂	40	16 by 16	55 by 55	Small buds	Ragweed ++++
11. S. R.	♂	48	11 by 15	50 by 50	None	Many false positive reactions
12. I. C.	♀	29	12 by 14	65 by 65	Small buds	Ragweed ++ (+) Grasses +++ House Dust ++
13. H. C.	♀	43	15 by 15	60 by 60	18	Ragweed ++++
14. C. E.	♀	37	14 by 15	60 by 60	None	Ragweed +++
15. J. E.	♂	33	15 by 15	55 by 60	None	Grasses +++
16. R. K.	♀	37	13 by 15	70 by 70	None	Ragweed ++++ House Dust +
17. W. H.	♂	40	15 by 15	50 by 50	None	Tree pollens +++
18. A. W.	♀	40	14 by 15	45 by 50	None	Grasses +++ Ragweed ++ House Dust +
19. A. L.	♀	31	13 by 14	50 by 65	Buds	Ragweed +++ House Dust ++
20. E. Z.	♀	39	17 by 17	60 by 70	None	Ragweed +++ Timothy +
21. O. H.	♀	39	14 by 15	60 by 70	None	Ragweed +++ House Dust +
22. DeW. Y.	♂	42	15 by 15	75 by 75	Buds	Ragweed +++ House Dust ++ Rabbit Dander ++ Feathers ++
23. J. McK.	♂	35	13 by 13	60 by 70	None	Tree Pollen + +
24. L. J.	♀	37	17 by 20	50 by 60	None	Grasses +++
25. O. Y.	♂	11	14 by 16	55 by 60	10	Grasses +++
26. H. C.	♀	39	11 by 12	80 by 100	None	Ragweed +++
27. J. McC.	♀	30	13 by 13	60 by 60	10	Ragweed ++ House Dust ++
28. W. C.	♂	36	16 by 18	60 by 70	Several small pseudopodia	Ragweed +++ House Dust ++ Rabbit Dander ++ Cat Dander ++ Horse Dander ++
29. S. Z.	♀	27	16 by 16	50 by 55	Small bud	Grasses +++
30. P. A.	♂	34	12 by 13	60 by 60	None	Ragweed +++
31. S. H.	♂	55	15 by 15	60 by 60	Several 10 mm. long	Ragweed +++ Grasses +++ House Dust ++
32. H. K.	♀	39	13 by 15	55 by 60	None	Ragweed +++
33. M. F.	♀	34	15 by 18	55 by 55	None	Ragweed +++ Timothy ++ House Dust ++
34. E. R.	♀	37	13 by 15	65 by 65	Buds	Ragweed +++
35. G. R.	♂	52	15 by 17	60 by 65	11	Ragweed +++
36. R. K.	♀	47	22 by 23	70 by 70	10	Ragweed +++ Grasses ++ Plaintain +++

TABLE I—CONT'D

PATIENT		AGE (YR.)	REACTION			
			HISTAMINE			ALLERGEN EXTRACT
			WHEAL (MM.)	FLARE (MM.)	PSEUDOPOD (MM.)	
37. E. R.	♀	30	10 by 15	55 by 55	None	Ragweed ++ Grasses ++
38. W. M.	♂	12	11 by 13	60 by 70	None	Ragweed +++ Cat Dander ++
39. M. K.	♀	35	12 by 14	70 by 70	None	Ragweed +++ House Dust +
40. M. B.	♂	50	13 by 13	50 by 55	Buds	Ragweed +++
41. J.R.	♂	18	14 by 15	50 by 70	Buds	Ragweed ++++ Grasses ++++
42. E. R.	♀	42	17 by 17	55 by 55	None	Ragweed ++++ House Dust ++
43. G. M.	♀	49	13 by 15	55 by 55	6	Ragweed ++++ House Dust ++
44. O. F.	♂	30	14 by 16	50 by 50	None	Ragweed +++ Grasses ++ Cat Dander ++
45. R. B.	♂	14	15 by 16	55 by 65	None	Ragweed +++ House Dust ++ Grasses ++
2. Bronchial asthma						
1. A. B.	♂	42	16 by 17	75 by 90	Small buds	Orris Root ++ House Dust +
2. M. V.	♀	37	18 by 20	45 by 55	15	Cat Dander +++ House Dust +
3. M. P.	♀	49	15 by 15	50 by 50	Small bud	Negative
4. P. P.	♂	24	15 by 15	50 by 50	6	Kapok ++ House Dust +
5. A. F.	♀	43	13 by 12	65 by 65	Small bud	Negative
6. M. B.	♂	48	13 by 14	50 by 55	None	Cat Dander ++ House Dust +
7. A. S.	♂	34	12 by 15	50 by 50	None	House Dust ++
8. A. M.	♂	47	13 by 15	60 by 60	None	Milk +
9. E. D.	♀	51	15 by 18	80 by 85	Small buds	Ragweed ++ Cat Dander +
10. R. N.	♀	22	15 by 15	40 by 50	5	Ragweed + House Dust +
11. A. M.	♀	56	13 by 20	50 by 50	9	Feathers + Plaintain +
12. R. K.	♂	15	12 by 12	50 by 70	None	House Dust ++ Horse Dander ++ Rabbit Dander ++ Cat Dander ++ Ragweed +++
13. F. G.	♂	69	13 by 20	60 by 70	None	Wheat +
14. F. J.	♀	46	15 by 21	70 by 80	10	Orris Root + Rice + Rye + Wool + Wheat +
3. Vasomotor rhinitis						
1. J. L.	♀	27	13 by 17	55 by 70	Buds	House Dust ++
2. K. T.	♀	47	13 by 21	65 by 70	Small buds	House Dust ±
3. M. P.	♀	21	14 by 15	50 by 50	Small bud	Negative
4. G. McG.	♀	44	11 by 13	45 by 45	None	Orris Root ++ House Dust + Sweet Vernal Grass ++
5. C. K.	♀	54	14 by 19	45 by 50	None	Goat Dander ±
6. L. P.	♀	51	14 by 14	65 by 65	None	Negative
7. R. G.	♀	28	12 by 15	40 by 40	Small bud	Negative
8. I. L.	♀	51	15 by 15	65 by 75	Small bud	Negative
9. R. C.	♀	42	11 by 12	50 by 55	None	Negative
10. A. T.	♀	18	11 by 15	60 by 60	None	Ragweed ++ Feathers ++ House Dust ++
4. Urticaria						
1. B. A.	♀	21	14 by 15	60 by 65	None	Negative
2. A. D.	♀	28	13 by 13	80 by 90	None	Ragweed ++ House Dust ++
3. T. S.	♀	21	16 by 17	60 by 65	None	Mustard +
5. Angioneurotic edema						
1. E. S.	♂	33	10 by 16		None	Negative
2. G. M.	♂	42	14 by 17	45 by 70	Buds	Negative
3. M. G.	♀	39	14 by 15	55 by 65	None	Negative
4. E. K.	♀	21	10 by 8		None	Not Tested
6. Migraine						
1. E. B.	♂	33	11 by 12	25 by 30	None	House Dust ++ Ragweed +++ Grasses ++

TABLE II

TOTALS FROM TABLE I

DIAGNOSIS	NUMBER OF PATIENTS	NUMBER OF PATIENTS WITH POSITIVE SPECIFIC SKIN TESTS	NUMBER OF PATIENTS WITH POSITIVE INTRADERMAL HISTAMINE TESTS
A. Nonallergic individuals	9	0	2
B. Allergic individuals			
Hay fever	45	45	7
Bronchial asthma	14	12	5
Vasomotor rhinitis	10	5	0
Urticaria	3	2	0
Migraine	1	1	0
Angioneurotic edema	4	0	0
Total	77	65	12

individuals examined by us gave a positive histamine reaction. However, in order to afford Atkinson's conception every possibility of confirmation we designated as positive a reaction in which there appeared a pseudopod of at least 5 mm. in length.

Eighty-six individuals were examined. Seventy-seven presented the clinical picture of allergy and in sixty-five of these cases specific skin tests were positive. Only twelve of these latter patients showed a positive histamine reaction according to the above definition. Nine individuals were suffering from nonallergic diseases; none of them had a positive specific skin reaction; two had positive reactions to histamine.

Table I summarizes the results of our skin tests.

CONCLUSIONS

It is not possible to differentiate allergic individuals from nonallergic ones by the use of an intradermal histamine test.

REFERENCE

1. Atkinson, M.: Observations on Etiology and Treatment of Ménière's Syndrome, J. A. M. A. **116**: 1753, 1941.

SEASONAL DERMATITIS DUE TO THE ALBUMIN FRACTION OF TIMOTHY POLLEN

JOHN H. MITCHELL, M.D., AND WILLIAM F. MITCHELL, M.D.
COLUMBUS, OHIO

AT THE meeting of the Mid-West Forum of Allergy held in St. Louis, January, 1944, Cooke[1] showed a photograph of a hay fever patient who had been previously treated with ragweed pollen successfully, and then returned a year or so later to begin treatment again. On the first dose of this second series of injections a large edematous inflammatory dermatitis appeared up and down the arm radiating from the point of injection of the aqueous ragweed pollen extract. Dr. Cooke mentioned that this reaction was due to the albumin fraction of the extract. This observation brought to mind one of our cases of seasonal dermatitis which we had been treating, and treating successfully, without knowing just how we were accomplishing the results.

CASE REPORT

Mrs. C. E. W., aged 21 years, consulted us Aug. 13, 1942, with a history of seasonal dermatitis for the previous seven years. Symptoms began in May or early June and lasted about six weeks. There was no dermatitis, asthma, or hay fever during this period or at any other time in the year. An older sister had been a patient of ours for several years because of ragweed asthma. The skin lesions began as fine papules over the arm, face, ears, upper chest, upper back, and neck. Itching was intense and later the whole skin area became erythematous, hot, and edematous, but there were no vesicles described in the history. In July the lesions gradually subsided and there was desquamation. The skin was quite clear during the rest of the year.

The history is presumptive evidence of contact dermatitis due to the oil of grass pollen. Both grass pollen oil and the oil obtained from the plant were applied to the skin but there were no positive reactions after seventy-two hours. There were no immediate wheal reactions to aqueous extract of grass, either by a scratch or intracutaneous technique. However, the day after the intracutaneous test, after using timothy pollen extract, 1:1,000, there was an area of dermatitis extending several inches from the point of the injection. This was an atypical contact type of dermatitis and we were greatly surprised to see this type of reaction, since we felt we were using a fat-free aqueous extract which had been washed several times with ether before the aqueous extraction was made. It was assumed that we must be dealing with a very minute amount of fat or lipoid material which had not come away with the ether washings and that this amount, although chemically infinitesimal, was biologically

quite active. Later, patch tests were made from blades of grass cut finely with a scissors and applied to the skin with adhesive. After forty-eight hours there was a positive skin reaction of the contact type, characterized by erythema, papules, and some underlying edema.

Since we obtained such a pronounced reaction with the aqueous solution we began using this material for treatment; 0.1 c.c. of 1:10,000 dilution was given subcutaneously in the same manner as we treat cases of grass hay fever. It was found, however, that after 0.3 c.c. was reached, the arm became so edematous and swollen that it was thought inadvisable to continue the injections beyond that point. Again and again gradual increases were attempted but always the large local reaction would be so distressing that we were forced to reduce the dose. Injections were given at intervals of two weeks throughout the winter and spring of 1943, and the results were quite satisfactory. Only very mild skin irritation was noticed during the grass pollinating season. The patient felt that she was 90 per cent better than she had been during the previous seven summers. The same injection interval was continued throughout 1943 and 1944, and a maximum dose of 0.3 c.c. of 1:10,000 aqueous timothy extract was given. During the 1944 season the patient noted only mild erythema on the flexural surfaces of the forearm which was not at all uncomfortable and she felt that she was 90 per cent, or more, improved.

After Dr. Cooke had shown us his case at the Allergy Forum in St. Louis, we wrote him and reported this case. He suggested that the albumin fraction might be the sensitizing agent and sent us a minute amount of albumin fraction of timothy pollen. This was applied to a small area on the patient's forearm by her family physician. Within forty-eight hours there appeared an area of vesiculation, 3 by 5 cm., surrounded by an area of edema and erythema, 10 by 15 cm.

DISCUSSION

This case presented the clinical characteristics and typical history and physical findings of contact dermatitis and its seasonal incidence corresponded exactly with the presence of grass pollen in the air. From previous knowledge one was justified in assuming that the oily fraction of the pollen was the chemical substance responsible for the dermatitis. In fact we were greatly surprised when the oily fraction obtained from timothy pollen did not react, while the intracutaneous administration of a minute amount of an aqueous fraction of timothy pollen produced a dermatitis which was clinically indistinguishable from that produced by contact allergens.

It is common practice for allergists and dermatologists to make patch tests with refined fatty or lipoid fractions of plants and other substances suspected of producing contact dermatitis. It is also generally agreed that in only 25 or 50 per cent of cases of clean-cut contact dermatitis can the cause of the dermatitis be proved by patch tests. May it not be possible that we have here an illustration of a newly discovered biologic

reaction and that it will be necessary to test by the patch method all cases of contact dermatitis with the original material unrefined or with an albuminous fraction as well as with a lipoid fraction.

Such cases as this must be of rare occurrence. This is the only one of its type we have seen in ten years of active allergy practice. We have seen several thousand cases of respiratory allergy due to the inhalation of grass and ragweed pollen and have not seen another individual sensitive to contact with the pollen. We have seen several cases of contact dermatitis due to the oily fraction of the ragweed plant and these were easily recognized and patch tests were obtained either to the natural plant leaf or to the oil obtained from ragweed plant or from ragweed pollen.

One also wonders, since this patient is sensitive to an albumin fraction, if there is a specific antibody which can be demonstrated in the blood. Since there was no immediate wheal reaction, one may assume no reagin would be present. Passive transfer tests were not done.

The response to therapy in this case was most satisfactory. This is in contrast with the results of therapy in cases of plant dermatitis where the oily fraction is given preseasonally for its prophylactic effect. It would be worth while to test cases of ragweed plant dermatitis with an albuminous fraction of ragweed pollen and if such cases gave a positive reaction of the contact type, one would be justified in treating them with the ordinary aqueous extracts used in the treatment of ragweed hay fever.

SUMMARY

1. A case of recurring seasonal dermatitis due to the albumin fraction of timothy pollen is reported.

2. We believe this case illustrates a hitherto unrecognized biologic reaction wherein a dermatitis of the contact type can be caused by the albuminous fraction rather than by the lipoid fraction.

REFERENCE

1. Cooke, Robert A.: A Consideration of Some Allergy Problems. I. Allergic Dermatitis (Eczema), J. ALLERGY **15**: 203, 1944.

ALLERGIC DERMATITIS DUE TO METALLIC COBALT*

LOUIS SCHWARTZ, M.D., AND SAMUEL M. PECK, M.D., BETHESDA, MD., AND KENNETH EDWIN BLAIR, M.D., AND KENNETH E. MARKUSON, M.D., DETROIT, MICH.

IN A manufacturing plant employing approximately 1,200 workers, there was a progressive increase in the number of cases of dermatitis since the plant had been in operation. The cases were not confined to any one department, but occurred in all parts of the plant. The U. S. Public Health Service was requested by the State Industrial Hygiene Bureau to trace the etiology of the eruption and to recommend preventive measures.

This plant manufactures cemented carbides, some of which are fabricated into cutting tools and dies. The cemented carbide materials are made from tungsten, tantalum, and titanium carbides, carbon, and metallic cobalt. The materials in powdered form are mixed in proper proportions, molded and pressed into the approximate shapes of the desired cutting edges, and fused in an electric furnace.

Inspection of Plant.—The cutting tools are of extreme hardness, and the abrasiveness of the dust from the fused cutting tool is second only to diamond dust. Indeed, diamond wheels are used to sharpen the cutting edges. Dust counts made throughout the plant by the State Industrial Hygiene Bureau have shown that considerable dust remains suspended in the air throughout the plant. This may account for the universal distribution of dermatitis. However, there is a greater concentration in the area called the metal room, where the ingredients composing the alloy are handled in the unfused powder form.

Dermatological Findings.—Approximately twenty patients with dermatitis were seen at the time of inspection. The patients worked in various parts of the plant, but the majority of them were employed in the metal room. The histories showed that they worked for one month, or more, before developing the dermatitis.

The eruption in a number of cases was limited to the antecubital spaces. In others it was found only on the sides of the neck and on the eyelids, while in still others the flexor portions of the forearms and the backs of the hands were affected. In a few patients the eruption was generalized.

The eruption in general was of the erythematous, papular type. Some of the lesions on the flexor surfaces of the forearms showed a ringed appearance with clearing centers and raised papular borders. In two patients who were employed as sweepers, a subacute, circumscribed patch

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of dermatitis was seen covering the external malleolus and extending over to the dorsum as well as over the ankle of one foot. This was the foot which was kept advanced as the sweepers collected the sweepings and was therefore exposed to the most dust.

The cases varied in severity, but in most instances they were mild enough to enable the workers to continue with their work. There were some instances of secondary infections due to scratching.

Patch tests were performed on six workers affected, with each of the ingredients used in the manufacture of the alloy, as well as with the loose powdery mixture of the unfused alloy. The patches were kept on for twenty-four hours and then read. They were again read for late reactions after forty-eight hours. There were no reactions from the oxides of tungsten, tantalum, and titanium, nor to the carbon. Positive patch tests were obtained on all six from the metallic cobalt powder, and the loose black powdery mixture containing all the metals. Two people not working in the plant were used as controls for the patch tests; there were no positive reactions from any of the patches.

The results of the patch tests show that sensitivity to cobalt is the cause of the dermatitis. The distribution of the eruption most marked a points of friction, such as around the ankles and in the flexors of the elbows as well as along the sides of the neck can be accounted for by the abrasive nature of the dust. This undoubtedly plays a role in the induction of sensitization.

Some of the workers who had been affected have recovered and developed a tolerance or "become hardened," which is a common finding in allergic, contact, occupational dermatitis.

Recommendations for Prevention.—1. The methods recommended by competent authorities for the abatement of dust throughout the plant should be installed.

2. The workers should wear protective sleeves made of dustproof material and fingerless gloves made of washable leather.

3. Face shields should be worn—this mainly to keep the soiled fingers from touching the face. If the face shields are not suitable for some of the operations, then protection ointments should be tried. The dry type of protective ointment which is made of a water insoluble resin dissolved in alcohol and containing an inert powder to reinforce the film of resin would probably offer better protection than a greasy type because it may hinder the action of the abrasive dust on the skin.[1]

4. Since the workers' clothes become saturated with the fine dust of the powdered alloys, it is advisable that the workers be furnished closely woven coveralls which are cleaned daily by the plant.

5. The workers should be given the opportunity of thoroughly washing up at noon and before going home.

6. Attention of the workers should be drawn to the fact that areas of skin such as bends of the elbows, the ankles, and other sites of fric-

tion or where the dusts tend to collect should be washed with special thoroughness.

7. Workers should be cautioned against touching the face with dust-soiled fingers because it is believed that it is chiefly in this manner that the face is affected.

SUMMARY

1. Dermatitis occurring among employees in a plant that manufactures cemented carbides was investigated.

2. Sensitivity to cobalt was found to be the cause of the dermatitis.

3. Recommendations for prevention are given.

REFERENCE

1. Schwartz, Louis: Protective Ointments and Industrial Cleansers, The Medical Clinics of North America, Philadelphia, 1942, W. B. Saunders Company.

Editorial

THE resignation of Will Cook Spain as secretary of the American Academy of Allergy has evoked widespread expressions of appreciation of his devotion. For twenty years, Dr. Spain not only served as secretary of the Association for the Study of Asthma and Allied Conditions, but he did this so efficiently that his long tenure was due to the insistence of each council that he continue. The work involved, especially during the years in which two meetings were held, grew heavy and detailed. This few realized because it was performed with apparent ease.

The process of amalgamation of the two constituent societies into the American Academy of Allergy made further demands on Dr. Spain's time. As secretary to the Academy during the important first year, his work was outstanding, and he conducted it with characteristic patience and good humor. In addition, he was chairman of the Merits Committee and was largely responsible for the arrangements of the recent annual meeting in New York.

Although Dr. Spain received some remuneration for expenses in conducting his office, he assembled this into a fund, and with the interest on this he established the Secretary's prize.

No more need be said to testify how indebted the Academy is to Will Spain. Although out of office and free from official responsibilities, there is little doubt but that he will be called upon in the future for his wise counsel and guidance. He carries with him the good wishes of all.

Fortunately for the Academy, the secretarial post has been transferred to the able hands of Dr. Karl Figley.

Correspondence

The Editor,
THE JOURNAL OF ALLERGY,

Dr. Feinberg's editorial in THE JOURNAL OF ALLERGY, September, 1944, on "Periarteritis Nodosa and Rheumatic Fever Manifestations," is very interesting and timely. It is our impression that another related disease entity should be included in this group; namely, acute disseminated lupus erythematosus or Libman-Sach's disease. In this disease, one finds related symptomatology, pathology, and possibly a similar etiology. The outstanding symptoms and findings are prolonged and

intermittent fever, arthritis, disseminated erythematous skin lesions, evidence of a depression of the bone marrow, serous membrane involvement, renal involvement (especially nephritis), lymphadenopathy, and cardiovascular involvement, the most characteristic being atypical verrucous endocarditis.

In this disease, one must also realize the potential danger of drug sensitivity, especially sensitivity to the sulfonamides. Recently, we saw a patient with disseminated lupus erythematosus who was given sulfonamides empirically. Shortly thereafter, he had a stormy course with death following in a few weeks. It is our belief that the sulfonamides have no place in the treatment of acute disseminated lupus erythematosus, and only after weighing the facts carefully should it be used cautiously in the complications. Pollack and Ziskind reported a case of a 14-year-old girl with disseminated lupus erythematosus who died during sulfonamide therapy.

In this disease, as in periarteritis nodosa and rheumatic fever, the etiology is not known; however, recent clinical observations and histopathologic findings suggest that it may be due to allergy or anaphylaxis —possibly related to the Schwartzman phenomenon.

Recently Fox reported a case of disseminated lupus erythematosus in a 17-year-old girl whose symptoms appeared shortly after receiving a prophylactic dose of antitetanic serum.

In a series of twenty-three post-mortem examinations of acute and subacute lupus erythematosus, Baehr, Klemperer, and Schiffrin found in twenty patients widespread visceral vascular lesions and in certain areas, including the skin, many capillaries, arterioles, and venules which showed endothelial proliferation often associated with thrombosis, necrosis, and hemorrhage, changes which are considered by the majority of pathologists (Wells) as evidence of an allergic reaction.

Klemperer and his co-workers believe that the basic alteration common to all lesions in disseminated lupus erythematosus whether in the viscera or blood vessels is "fibrinoid degeneration of collagen." Similar changes were noted by Rich and Gregory in rabbits with experimental serum sickness who developed cardiac lesions that resembled those of rheumatic carditis. Gerlach in his work on the Arthus phenomenon considers fibrinoid degeneration an essential feature of hyperergic inflammation.

There are some who believe that a similar process but with varied anatomic distribution occurs in scleroderma and thromboangiitis obliterans.

—Major Simon S. Rubin, M.C.

Annual Meeting

THE AMERICAN ACADEMY OF ALLERGY

The first annual meeting of the Academy was held at the Waldorf-Astoria Hotel in New York on December 11 and 12. The program was followed essentially as printed in the September issue of THE JOURNAL. There was a large attendance. Papers presented at the meeting will be published in subsequent numbers of THE JOURNAL, beginning with the March issue. Reports of committee transactions and other business of interest to members will appear in this section.

The Executive Committee, acting as the Publications Committee, elected Dr. Sanford B. Hooker to the Editorial Board of THE JOURNAL OF ALLERGY. Dr. Hooker, Professor of Immunology at Boston University, an editor of the Journal of Immunology, and President of the Socity for the Study of Asthma and Allied Conditions in 1935, is well known for his distinguished work in immunology and immunochemistry. Dr. Hooker will pass on manuscripts which deal with these phases of allergy.

The Merits Committee, Dr. Spain, Chairman, and Drs. Hooker, Feinberg, and Alexander, awarded the Secretary's prize to Dr. Harvey J. Black for the paper of its selection among those presented at the Annual Meeting of the Academy. The decision was unanimous.

The committee voted to withhold the Marcelle award and the Abbott award this year.

The Academy, in conjunction with Columbia University, is offering a postgraduate course for one week in New York City, beginning Feb. 26, 1945. Announcement of this course will be found on the advertising pages of this issue of THE JOURNAL and the purpose of it outlined in the report of the committee on Education, under this section.

Several members of the Academy participated in the organization of the Pittsburgh Allergy Society. Dr. Leo H. Criep was elected President and Dr. James A. Mansmann, Secretary-Treasurer. Any physician in that locality practicing allergy is cordially invited to join.

Report of the Committee on Education for Year Ending Dec. 5, 1944

In accordance with the constitution and bylaws of the American Academy of Allergy, a Committee on Education was created.

The first step to be taken was a study of the entire field of education in allergy and, in line with this, each member was requested to supply information on the existing and potential facilities of current and customary prewar educational activity in that institution with which he is presently connected. Mimeographs of all replies were sent to officers and committee members for their information and study, together with the following explanatory letter from the Chairman, dated March 1, 1944, which read in part as follows: "To clarify the situation, the following points should be kept in mind: (1) our studies and plans must be made with an eye to the post-war period more than to the immediate present. (2) In our communications we must conform to the accepted terminology of medical circles as follows: Undergraduate education is self-explanatory. Graduate medical education means the period of education immediately following graduation from an undergraduate medical school and so includes for the most part, internships, residencies, and fellowships (both citizens and foreigners). Postgraduate education includes all types of medical education after starting in practice. Under this comes attendance at meetings and demonstrations and the refresher courses. It applies to specialists as well as general practitioners from home or abroad."

"It is then for these three fields—undergraduate, graduate and postgraduate that we should now lay our plans for the future. For efficiency's sake and in conformity with the above division of educational fields, your chairman is now dividing the Committee on Education of the American Academy of Allergy into three subcommittees as follows:"

Undergraduate	*Graduate*	*Postgraduate*
Dr. Oscar Swineford, chairman	Dr. Francis Rackemann, chairman	Dr. Robert Cooke, chairman
Dr. Robert Benson	Dr. Harry Alexander	Dr. J. Harvey Black
Dr. Stearns Bullen	Dr. Horace Baldwin	Dr. Aaron Brown
Dr. Leo Criep	Dr. Wyndham Blanton	Dr. Robert Chobot
Dr. Samuel Feinberg	Dr. Albert Rowe	Dr. Milton Cohen
Dr. Leslie Gay	Dr. Louis Tuft	Dr. Will C. Spain
Dr. Robert Cooke	Dr. Robert Cooke	Dr. Matthew Walzer

On Oct. 22, 1944, a preliminary meeting of the Committee was held in New York City for a consideration of the reports of the three subcommittees.

1. *Report on Undergraduate Education.*—Dr. Swineford had sent an extensive questionnaire to the deans of sixty-six class "A" medical schools. The fifty-five replies are summarized as follows:

48 medical schools include allergy as a sub-division of the Department of Medicine.

49 medical schools have an Allergy Clinic. From one to ten members of the teaching staff have allergy as a chief interest.
46 medical schools use the Allergy Clinic for teaching.
24 medical schools rotate all students through the Allergy Clinic.
20 medical schools have allergy instruction as an elective, but in twelve schools this is an elective course for more detailed study.
51 medical schools have didactic lectures in allergy for all students.
38 medical schools have only clinical instruction given by a specialist in allergy.
34 medical schools showed an increase in allergy instruction over the past five years.
25 medical schools plan increased instruction in allergy after the war.

This information disclosed the wide variation that exists in the best American medical schools in the undergraduate teaching of allergy and it is the opinion of this committee that in the great majority, it is inadequate. It is significant that in 51 schools all students have at least some didactic instruction in allergy, that in 34 schools there has been an increasing amount of instruction during the past five years, and that 25 schools are planning for increased facilities after the war. It is obvious, however, that much remains to be done toward even limited and elementary undergraduate instruction in the principles and practices of allergy in the majority of our medical schools.

2. *Report on Graduate Instruction.*—a. Interns: A survey shows that it has not been customary to utilize the facilities of the Allergy Clinic, where one exists, in the majority of the medical services in hospitals which are listed by the American Medical Association as "approved for the training of interns." With the present one-year internship, it would be impossible even if desirable.

b. Residents and Fellows in Allergy: A careful survey was made of this field by a committee under the chairmanship of Dr. Matthew Walzer and published in THE JOURNAL OF ALLERGY **13**: 508, 1942. At that time there were but twelve institutions engaged in training graduates as fellows or residents in allergy, and in only five was the period of training over one year. There were a total of seventy-six hospitals with Allergy Clinics in which such facilities might at that time have been developed, but at present there are even fewer physicians in such graduate positions on account of the personnel shortage incident to the war.

3. *Report on Postgraduate Education.*—Dr. Walzer's 1942 report listed ten short postgraduate courses. Today there are very few organized and functioning courses for formal education in allergy for the postgraduate student. A demand exists but teachers are scarce. Dr. Spain has continued his three-week course at Postgraduate Hospital. Last October certain Fellows of this Academy gave a one week

course in New York City for the American College of Physicians. There were sixty-five registrants for this course.

During the past year this Committee has also assisted the Co-ordinator of Inter-American Affairs and the Pan American Sanitary Committee of the Pan American Association in placing in allergy clinics physicians from South America and Cuba who were brought to this country on fellowships for special medical study.

So much for the situation of allergy education as it exists at present and now for a look at the future.

It must be expected that the transition from a war to peace status will probably be gradual rather than sudden—that the potential medical students and the Medical Reserve Corps will be released only as their need for the Armed Forces decreases—hence the educational movement will develop gradually but with increasing tempo. We must be ready to meet it; hence the planning and groundwork must be done now.

1. *Undergraduate Education.*—The Committee is unanimous in its feeling that it is highly desirable that the medical student should receive training in the fundamentals of immunologic and clinical allergy. In the majority of medical schools it has been inadequate. We shall pursue a more detailed study of allergy undergraduate teaching with the aid of instructors who are willing to cooperate in order to outline at least a minimal desirable curriculum. It must be expected that results will come slowly.

2. *Graduate Education.*—The utilization of interns on a rotating service through the allergy clinic has never proved beneficial to interns or the clinic. For their one or two years in the hospital, medical interns should give their entire time and thought to internal medicine and special fields should not be allowed to interfere with the opportunity to acquire a sound medical foundation.

The years following internship, however, afford great opportunity for further study in the recognized subspecialties of medicine. Residencies, assistant residencies, and fellowships in allergy should be made available and must be made adequate—more adequate than in the past—to be attractive. Such positions for advanced study in allergy should be open only to those who have had two years of general medical training and should continue for at least two, and preferably three, years. During this time contact with internal medicine must be maintained through the clinic, the ward, clinico-pathologic conferences, and lectures. Thus, the young physician is prepared for his future in clinical medicine and allergy and equipped for the examination for certification as a specialist in medicine and allergy at one and the same time. In addition, fellowships in pathology, chemistry, immunology, bacteriology, and physiology must be considered for those who prefer to perfect themselves in scientific and laboratory research rather than clinical allergy.

Naturally there will be a useful field for other less intensive courses than that outlined but an assured future for allergy demands the highest type of training for those men upon whom its teaching and research must depend.

It must not be inferred that such intensive training is the only procedure deemed satisfactory or that it is essential to qualify for examination for certification. The Advisory Committee has previously outlined several alternatives as published in THE JOURNAL OF ALLERGY **14**: 91, 1942.

3. *Postgraduate Education.*—In this field there are a great many possibilities, for here there are no such restrictions as those imposed by limited time and the disposition of the teachers and heads of medical services during undergraduate and intern education. The postgraduate student is free to choose his own educational line.

We shall plan refresher courses for the specialists in allergy and courses for the general practitioners who wish to use the procedures and principles of allergy to their own and the patient's advantage. This calls for different types and grades of instruction for varying periods of time and in various sections of the country.

Already planned is an advanced course of one week for those who have studied and practiced allergy. It will be given the latter part of February under the auspices of Columbia University and the American Academy of Allergy at the Postgraduate Hospital in New York, with Dr. Spain directing. The course will consist of several lectures for the entire body of registrants each morning. The afternoons will be devoted to colloquia, with one instructor for each of a number of small groups. Each registrant will thus have an opportunity to cover the field of clinical allergy in an intimate and informal manner. The fee for this course has been set at $100.00. A certain number of places are to be reserved for medical officers of the Army, Navy, and Public Health Service, free of charge. Notices will appear shortly in the Journal of the American Medical Association, the Annals of Internal Medicine and THE JOURNAL OF ALLERGY. Applications with a deposit of $25.00 may be made now.

Through the medium of our JOURNAL OF ALLERGY, the Committee on Education will keep you advised on all plans as they become crystallized, not only for courses but for all developments within its sphere. We would be glad to act also as a clearing house of information for those who have positions open or for trained physicians seeking further opportunities. In all things pertaining to education, your committee will be glad to be of service to each one of you.

Respectfully submitted,

ROBERT A. COOKE, CHAIRMAN
Committee on Education.